(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

B3

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/10199 A2

(51) International Patent Classification[7]: C07K 14/00

(21) International Application Number: PCT/US01/23232

(22) International Filing Date: 24 July 2001 (24.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/222,504 2 August 2000 (02.08.2000) US
09/728,787 28 November 2000 (28.11.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/10199 A2

(54) Title: C3B/C4B COMPLEMENT RECEPTOR-LIKE MOLECULES AND USES THEREOF

(57) Abstract: Novel C3b/C4b CR-like polypeptides and nucleic acid molecules encoding the same. The invention also provides vectors, host cells, selective binding agents, and methods for producing C3b/C4b CR-like polypeptides. Also provided for are methods for the treatment, diagnosis, amelioration, or prevention of diseases with C3b/C4b CR-like polypeptides.

C3B/C4B COMPLEMENT RECEPTOR-LIKE MOLECULES AND USES THEREOF

This application claims the benefit of U.S. Provisional Application No. 60/222,504, filed August 2, 2000 and U.S. Application No. 09/728,787 filed November 28, 2000, which are hereby incorporated by reference.

Field of the Invention

The present invention relates to novel C3b/C4b Complement Receptor-like polypeptides and nucleic acid molecules encoding the same. The invention also relates to vectors, host cells, pharmaceutical compositions, selective binding agents and methods for producing C3b/C4b Complement Receptor-like polypeptides. Also provided for are methods for the diagnosis, treatment, amelioration, and/or prevention of diseases associated with C3b/C4b Complement Receptor-like polypeptides.

Background of the Invention

Technical advances in the identification, cloning, expression and manipulation of nucleic acid molecules and the deciphering of the human genome have greatly accelerated the discovery of novel therapeutics. Rapid nucleic acid sequencing techniques can now generate sequence information at unprecedented rates and, coupled with computational analyses, allow the assembly of overlapping sequences into partial and entire genomes and the identification of polypeptide-encoding regions. A comparison of a predicted amino acid

sequence against a database compilation of known amino acid sequences allows one to determine the extent of homology to previously identified sequences and/or structural landmarks. The cloning and expression of a polypeptide-encoding region of a nucleic acid molecule provides a polypeptide product for structural and functional analyses. The manipulation of nucleic acid molecules and encoded polypeptides may confer advantageous properties on a product for use as a therapeutic.

Despite the significant technical advances in genome research over the past decade, the potential for the development of novel therapeutics based on the human genome is still largely unrealized. Many genes encoding potentially beneficial polypeptide therapeutics, or those encoding polypeptides, which may act as "targets" for therapeutic molecules, have still not been identified.

Accordingly, it is an object of the invention to identify novel polypeptides and nucleic acid molecules encoding the same, which have diagnostic or therapeutic benefit.

Summary of the Invention

The present invention relates to novel C3b/C4b Complement Receptor-like nucleic acid molecules and encoded polypeptides.

The invention provides for an isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence as set forth in SEQ

ID NO:1, SEQ ID NO:3, or SEQ ID NO:6;

(b) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of (a) or (b), wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(d) a nucleotide sequence complementary to any of (a)-(c).

The invention also provides for an isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(b) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, (a), or (b) encoding a polypeptide fragment of at least about 25 amino acid

residues, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, or (a)-(c) comprising a fragment of at least about 16 nucleotides;

(e) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a)-(d), wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(f) a nucleotide sequence complementary to any of (a)-(e).

The invention further provides for an isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(b) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid insertion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid deletion, wherein the

polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 which has a C- and/or N- terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(e) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(f) a nucleotide sequence of (a)-(e) comprising a fragment of at least about 16 nucleotides;

(g) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a)-(f), wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(h) a nucleotide sequence complementary to any of (a)-(e).

The invention also provides for an isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) an amino acid sequence of the mature C3b/C4b Complement Receptor-like polypeptide wherein the

polypeptide comprises the amino acid sequence contained within SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, and optionally further comprises an amino-terminal methionine;

(b) an amino acid sequence for an ortholog of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) an amino acid sequence that is at least about 70, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) a fragment of the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 comprising at least about 25 amino acid residues, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(e) an amino acid sequence for an allelic variant or splice variant of either the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or at least one of (a)-(c) wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

The invention further provides for an isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(b) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid insertion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid deletion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 which has a C- and/or N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(e) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

Also provided are fusion polypeptides comprising the amino acid sequences of (a)-(e) above.

The present invention also provides for an expression vector comprising the isolated nucleic acid molecules as set forth herein, recombinant host cells comprising recombinant nucleic acid molecules as set forth herein, and a method of producing a C3b/C4b Complement Receptor-like polypeptide comprising culturing the host cells and optionally isolating the polypeptide so produced.

A transgenic non-human animal comprising a nucleic acid molecule encoding a C3b/C4b Complement Receptor-like polypeptide is also encompassed by the invention. The C3b/C4b Complement Receptor-like nucleic acid molecules are introduced into the animal in a manner that allows expression and increased levels of the C3b/C4b Complement Receptor-like polypeptide, which may include increased circulating levels. The transgenic non-human animal is preferably a mammal.

Also provided are derivatives of the C3b/C4b Complement Receptor-like polypeptides of the present invention.

Additionally provided are selective binding agents such as antibodies and peptides capable of specifically binding the C3b/C4b Complement Receptor-like polypeptides of the invention. Such antibodies and peptides may be agonistic or antagonistic.

Pharmaceutical compositions comprising the nucleotides, polypeptides, or selective binding agents of the present invention and one or more pharmaceutically acceptable formulation agents are also encompassed by the invention. The pharmaceutical compositions are used to provide therapeutically effective amounts of the nucleotides or polypeptides of

the present invention. The invention is also directed to methods of using the polypeptides, nucleic acid molecules, and selective binding agents.

The C3b/C4b Complement Receptor-like polypeptides and nucleic acid molecules of the present invention may be used to treat, prevent, ameliorate, and/or detect diseases and disorders, including those recited herein.

The present invention also provides a method of assaying test molecules to identify a test molecule which binds to a C3b/C4b Complement Receptor-like polypeptide. The method comprises contacting a C3b/C4b Complement Receptor-like polypeptide with a test molecule and determining the extent of binding of the test molecule to the polypeptide. The method further comprises determining whether such test molecules are agonists or antagonists of a C3b/C4b Complement Receptor-like polypeptide. The present invention further provides a method of testing the impact of molecules on the expression of C3b/C4b Complement Receptor-like polypeptide or on the activity of C3b/C4b Complement Receptor-like polypeptide.

Methods of regulating expression and modulating (*i.e.*, increasing or decreasing) levels of a C3b/C4b Complement Receptor-like polypeptide are also encompassed by the invention. One method comprises administering to an animal a nucleic acid molecule encoding a C3b/C4b Complement Receptor-like polypeptide. In another method, a nucleic acid molecule comprising elements that regulate or modulate the expression of a C3b/C4b Complement Receptor-like polypeptide may be administered. Examples of these

methods include gene therapy, cell therapy, and anti-sense therapy as further described herein.

The C3b/C4b Complement Receptor-like polypeptide can be used for identifying ligands thereof. Various forms of "expression cloning" have been used for cloning ligands for receptors. *See e.g.*, Davis *et al.*, *Cell*, 87:1161-1169 (1996). These and other C3b/C4b Complement Receptor-like ligand cloning experiments are described in greater detail herein. Isolation of the C3b/C4b Complement Receptor-like ligand(s) allows for the identification or development of novel agonists and/or antagonists of the C3b/C4b Complement Receptor-like signaling pathway. Such agonists and antagonists include C3b/C4b Complement Receptor-like ligand(s), anti-C3b/C4b Complement Receptor-like ligand antibodies and derivatives thereof, small molecules, or antisense oligonucleotides, any of which can be used for potentially treating one or more diseases or disorders, including those recited herein.

Brief Description of the Figures

Figure 1 depicts a nucleic acid sequence (SEQ ID NO:1) encoding human C3b/C4b Complement Receptor-like polypeptide. Also depicted is the amino acid sequence (SEQ ID NO:2) of human C3B/C4b Complement Receptor-like polypeptide.

Figure 2 depicts a nucleic acid sequence (SEQ ID NO:6) encoding a second human C3b/C4b Complement Receptor-like polypeptide. Also depicted is the amino acid sequence (SEQ ID NO:7) of human C3B/C4b Complement Receptor-like polypeptide.

Figure 3 depicts a nucleic acid sequence (SEQ ID NO:3) encoding rat C3b/C4b Complement Receptor-like polypeptide. Also depicted is the amino acid sequence of rat C3b/C4b Complement Receptor-like polypeptide (SEQ ID NO:4).

Figure 4 depicts an amino acid comparison of a known human C3b/C4b Complement Receptor (SEQ ID NO:5) and the human AGP-41773 (SEQ ID NO:2).

Detailed Description of the Invention

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All references cited in this application are expressly incorporated by reference herein.

Definitions

The term "C3b/C4b Complement Receptor-like" is abbreviated herein as "C3b/C4b CR-like" and is also referred to as "AGP-41773". The terms "C3b/C4b CR-like gene" or "C3b/C4b CR-like nucleic acid molecule" or "polynucleotide" refers to a nucleic acid molecule comprising or consisting of a nucleotide sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, and nucleic acid molecules as defined herein.

The term "C3b/C4b CR-like polypeptide" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, and related polypeptides. Related polypeptides include: C3b/C4b CR-like polypeptide allelic variants, C3b/C4b CR-like

polypeptide orthologs, C3b/C4b CR-like polypeptide splice variants, C3b/C4b CR-like polypeptide variants and C3b/C4b CR-like polypeptide derivatives. C3b/C4b CR-like polypeptides may be mature polypeptides, as defined herein, and may or may not have an amino terminal methionine residue, depending on the method by which they are prepared.

The term "C3b/C4b CR-like polypeptide allelic variant" refers to one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms.

The term "C3b/C4b CR-like polypeptide derivatives" refers to the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, C3b/C4b CR-like polypeptide allelic variants, C3b/C4b CR-like polypeptide orthologs, C3b/C4b CR-like polypeptide splice variants, or C3b/C4b CR-like polypeptide variants, as defined herein, that have been chemically modified.

The term "C3b/C4b CR-like polypeptide fragment" refers to a polypeptide that comprises a truncation at the amino terminus (with or without a leader sequence) and/or a truncation at the carboxy terminus of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, C3b/C4b CR-like polypeptide allelic variants, C3b/C4b CR-like polypeptide orthologs, C3b/C4b CR-like polypeptide splice variants and/or a C3b/C4b CR-like polypeptide variant having one or more amino acid additions or substitutions or internal deletions (wherein the resulting polypeptide is at

least 6 amino acids or more in length) as compared to the C3b/C4b CR-like polypeptide amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7. C3b/C4b CR-like polypeptide fragments may result from alternative RNA splicing or from *in vivo* protease activity. For transmembrane or membrane-bound forms of a C3b/C4b CR-like polypeptide, preferred fragments include soluble forms such as those lacking a transmembrane or membrane-binding domain. In preferred embodiments, truncations comprise about 10 amino acids, or about 20 amino acids, or about 50 amino acids, or about 75 amino acids, or about 100 amino acids, or more than about 100 amino acids. The polypeptide fragments so produced will comprise about 25 contiguous amino acids, or about 50 amino acids, or about 75 amino acids, or about 100 aminc acids, or about 150 amino acids, or about 200 amino acids. Such C3b/C4b CR-like polypeptide fragments may optionally comprise an amino terminal methionine residue. It will be appreciated that such fragments can be used, for example, to generate antibodies to C3b/C4b CR-like polypeptides.

The term "C3b/C4b CR-like fusion polypeptide" refers to a fusion of one or more amino acids (such as a heterologous peptide or polypeptide) at the amino or carboxy terminus of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, C3b/C4b CR-like polypeptide allelic variants, C3b/C4b CR-like polypeptide orthologs, C3b/C4b CR-like polypeptide splice variants, or C3b/C4b CR-like polypeptide variants having one or more amino acid deletions, substitutions or internal additions as compared to the C3b/C4b CR-like polypeptide amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

The term "C3b/C4b CR-like polypeptide ortholog" refers to a polypeptide from another species that corresponds to C3b/C4b CR-like polypeptide amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7. For example, mouse and human C3b/C4b CR-like polypeptides are considered orthologs of each other.

The term "C3b/C4b CR-like polypeptide splice variant" refers to a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of C3b/C4b CR-like polypeptide amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

The term "C3b/C4b CR-like polypeptide variants" refers to C3b/C4b CR-like polypeptides comprising amino acid sequences having one or more amino acid sequence substitutions, deletions (such as internal deletions and/or C3b/C4b CR-like polypeptide fragments), and/or additions (such as internal additions and/or C3b/C4b CR-like fusion polypeptides) as compared to the C3b/C4b CR-like polypeptide amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 (with or without a leader sequence). Variants may be naturally occurring (*e.g.*, C3b/C4b CR-like polypeptide allelic variants, C3b/C4b CR-like polypeptide orthologs and C3b/C4b CR-like polypeptide splice variants) or artificially constructed. Such C3b/C4b CR-like polypeptide variants may be prepared from the corresponding nucleic acid molecules having a DNA sequence that varies accordingly from the DNA sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6. In preferred embodiments, the variants have from

1 to 3, or from 1 to 5, or from 1 to 10, or from 1 to 15, or from 1 to 20, or from 1 to 25, or from 1 to 50, or from 1 to 75, or from 1 to 100, or more than 100 amino acid substitutions, insertions, additions and/or deletions, wherein the substitutions may be conservative, or non-conservative, or any combination thereof.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antibody, and additionally capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. An antigen may have one or more epitopes.

The term "biologically active C3b/C4b CR-like polypeptides" refers to C3b/C4b CR-like polypeptides having at least one activity characteristic of the polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

The terms "effective amount" and "therapeutically effective amount" each refer to the amount of a C3b/C4b CR-like polypeptide or C3b/C4b CR-like nucleic acid molecule used to support an observable level of one or more biological activities of the C3b/C4b CR-like polypeptides as set forth herein.

The term "expression vector" refers to a vector which is suitable for use in a host cell and contains nucleic acid sequences which direct and/or control the expression of heterologous nucleic acid sequences. Expression includes, but is not limited to, processes

such as transcription, translation, and RNA splicing, if introns are present.

The term "host cell" is used to refer to a cell which has been transformed, or is capable of being transformed with a nucleic acid sequence and then of expressing a selected gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent, so long as the selected gene is present.

The term "identity" as known in the art, refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between nucleic acid molecules or polypeptides, as the case may be, as determined by the match between strings of two or more nucleotide or two or more amino acid sequences. "Identity" measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., "algorithms").

The term "similarity" is a related concept, but in contrast to "identity", refers to a measure of similarity which includes both identical matches and conservative substitution matches. If two polypeptide sequences have, for example, 10/20 identical amino acids, and the remainder are all non-conservative substitutions, then the percent identity and similarity would both be 50%. If in the same example, there are 5

more positions where there are conservative substitutions, then the percent identity remains 50%, but the per cent similarity would be 75% (15/20). Therefore, in cases where there are conservative substitutions, the degree of similarity between two polypeptides will be higher than the percent identity between those two polypeptides.

The term "isolated nucleic acid molecule" refers to a nucleic acid molecule of the invention that (1) has been separated from at least about 50 percent of proteins, lipids, carbohydrates or other materials with which it is naturally found when total DNA is isolated from the source cells, (2) is not linked to all or a portion of a polynucleotide to which the "isolated nucleic acid molecule" is linked in nature, (3) is operably linked to a polynucleotide which it is not linked to in nature, or (4) does not occur in nature as part of a larger polynucleotide sequence. Preferably, the isolated nucleic acid molecule of the present invention is substantially free from any other contaminating nucleic acid molecule(s) or other contaminants that are found in its natural environment that would interfere with its use in polypeptide production or its therapeutic, diagnostic, prophylactic or research use.

The term "isolated polypeptide" refers to a polypeptide of the present invention that (1) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates or other materials with which it is naturally found when isolated from the source cell, (2) is not linked (by covalent or noncovalent interaction) to all or a

portion of a polypeptide to which the "isolated polypeptide" is linked in nature, (3) is operably linked (by covalent or noncovalent interaction) to a polypeptide with which it is not linked in nature, or (4) does not occur in nature. Preferably, the isolated polypeptide is substantially free from any other contaminating polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic or research use.

The term "mature C3b/C4b CR-like polypeptide" refers to a C3b/C4b CR-like polypeptide lacking a leader sequence. A mature C3b/C4b CR-like polypeptide may also include other modifications such as proteolytic processing of the amino terminus (with or without a leader sequence) and/or the carboxy terminus, cleavage of a smaller polypeptide from a larger precursor, N-linked and/or O-linked glycosylation, and the like.

The term "nucleic acid sequence" or "nucleic acid molecule" refers to a DNA or RNA sequence. The term encompasses molecules formed from any of the known base analogs of DNA and RNA such as, but not limited to 4-acetylcytosine, 8-hydroxy-N6-methyladenosine, aziridinyl-cytosine, pseudoisocytosine, 5-(carboxyhydroxylmethyl) uracil, 5-fluorouracil, 5-bromouracil, 5-carboxymethylaminomethyl-2-thiouracil, 5-carboxy-methylaminomethyluracil, dihydrouracil, inosine, N6-iso-pentenyladenine, 1-methyladenine, 1-methylpseudouracil, 1-methylguanine, 1-methylinosine, 2,2-dimethyl-guanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-methyladenine,

7-methylguanine, 5-methylaminomethyluracil, 5-methoxyamino-methyl-2-thiouracil, beta-D-mannosylqueosine, 5' -methoxycarbonyl-methyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, oxybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, N-uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, pseudouracil, queosine, 2-thiocytosine, and 2,6-diaminopurine.

The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by man. Similarly, "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by man.

The term "operably linked" is used herein to refer to an arrangement of flanking sequences wherein the flanking sequences so described are configured or assembled so as to perform their usual function. Thus, a flanking sequence operably linked to a coding sequence may be capable of effecting the replication, transcription and/or translation of the coding sequence. For example, a coding sequence is operably linked to a promoter when the promoter is capable of directing transcription of that coding sequence. A flanking sequence need not be contiguous with the coding sequence, so long as it functions correctly. Thus, for example, intervening untranslated yet

transcribed sequences can be present between a promoter sequence and the coding sequence and the promoter sequence can still be considered "operably linked" to the coding sequence.

The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation materials suitable for accomplishing or enhancing the delivery of the C3b/C4b CR-like polypeptide, C3b/C4b CR-like nucleic acid molecule or C3b/C4b CR-like selective binding agent as a pharmaceutical composition.

The term "selective binding agent" refers to a molecule or molecules having specificity for a C3B/C4B CR-like polypeptide. As used herein, the terms, "specific" and "specificity" refer to the ability of the selective binding agents to bind to human C3b/C4b CR-like polypeptides and not to bind to human non-C3b/C4b CR-like polypeptides. It will be appreciated, however, that the selective binding agents may also bind orthologs of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, that is, interspecies versions thereof, such as mouse and rat polypeptides.

The term "transduction" is used to refer to the transfer of genes from one bacterium to another, usually by a phage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by retroviruses.

The term "transfection" is used to refer to the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has

been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. See, for example, Graham *et al.*, *Virology*, 52:456 (1973); Sambrook *et al.*, *Molecular Cloning, a laboratory Manual*, Cold Spring Harbor Laboratories (New York, 1989); Davis *et al.*, *Basic Methods in Molecular Biology*, Elsevier, 1986; and Chu *et al.*, *Gene*, 13:197 (1981). Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

The term "transformation" as used herein refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain a new DNA. For example, a cell is transformed where it is genetically modified from its native state. Following transfection or transduction, the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, may be maintained transiently as an episomal element without being replicated, or may replicate independently as a plasmid. A cell is considered to have been stably transformed when the DNA is replicated with the division of the cell.

The term "vector" is used to refer to any molecule (*e.g.*, nucleic acid, plasmid, or virus) used to transfer coding information to a host cell.

Relatedness of Nucleic Acid Molecules and/or Polypeptides

It is understood that related nucleic acid molecules include allelic or splice variants of the nucleic acid molecule of SEQ ID NO:1, SEQ ID NO:3, or

SEQ ID NO:6, and include sequences which are complementary to any of the above nucleotide sequences. Related nucleic acid molecules also include a nucleotide sequence encoding a polypeptide comprising or consisting essentially of a substitution, modification, addition and/or a deletion of one or more amino acid residues compared to the polypeptide in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

Fragments include molecules which encode a polypeptide of at least about 25 amino acid residues, or about 50, or about 75, or about 100, or greater than about 100 amino acid residues of the polypeptide of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

In addition, related C3b/C4b CR-like nucleic acid molecules include those molecules which comprise nucleotide sequences which hybridize under moderately or highly stringent conditions as defined herein with the fully complementary sequence of the nucleic acid molecule of SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, or of a molecule encoding a polypeptide, which polypeptide comprises the amino acid sequence as shown in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or of a nucleic acid fragment as defined herein, or of a nucleic acid fragment encoding a polypeptide as defined herein. Hybridization probes may be prepared using the C3b/C4b CR-like sequences provided herein to screen cDNA, genomic or synthetic DNA libraries for related sequences. Regions of the DNA and/or amino acid sequence of C3b/C4b CR-like polypeptide that exhibit significant identity to known sequences are readily determined using sequence alignment algorithms as

described herein and those regions may be used to design probes for screening.

The term "highly stringent conditions" refers to those conditions that are designed to permit hybridization of DNA strands whose sequences are highly complementary, and to exclude hybridization of significantly mismatched DNAs. Hybridization stringency is principally determined by temperature, ionic strength, and the concentration of denaturing agents such as formamide. Examples of "highly stringent conditions" for hybridization and washing are 0.015M sodium chloride, 0.0015M sodium citrate at 65-68°C or 0.015M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42°C. See Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, (Cold Spring Harbor, N.Y. 1989); Anderson *et al.*, Nucleic Acid Hybridisation: a practical approach, Ch. 4, IRL Press Limited (Oxford, England).

More stringent conditions (such as higher temperature, lower ionic strength, higher formamide, or other denaturing agent) may also be used, however, the rate of hybridization will be affected. Other agents may be included in the hybridization and washing buffers for the purpose of reducing non-specific and/or background hybridization. Examples are 0.1% bovine serum albumin, 0.1% polyvinyl-pyrrolidone, 0.1% sodium pyrophosphate, 0.1% sodium dodecylsulfate ($NaDodSO_4$ or SDS), ficoll, Denhardt's solution, sonicated salmon sperm DNA (or other non-complementary DNA), and dextran sulfate, although other suitable agents can also be used. The concentration and types of these additives

can be changed without substantially affecting the stringency of the hybridization conditions. Hybridization experiments are usually carried out at pH 6.8-7.4, however, at typical ionic strength conditions, the rate of hybridization is nearly independent of pH. See Anderson *et al.*, Nucleic Acid Hybridisation: a Practical Approach, Ch. 4, IRL Press Limited (Oxford, England).

Factors affecting the stability of a DNA duplex include base composition, length, and degree of base pair mismatch. Hybridization conditions can be adjusted by one skilled in the art in order to accommodate these variables and allow DNAs of different sequence relatedness to form hybrids. The melting temperature of a perfectly matched DNA duplex can be estimated by the following equation:

$$T_m(^\circ C) = 81.5 + 16.6(\log[Na+]) + 0.41(\%G+C) - 600/N - 0.72(\%formamide)$$

where N is the length of the duplex formed, [Na+] is the molar concentration of the sodium ion in the hybridization or washing solution, %G+C is the percentage of (guanine+cytosine) bases in the hybrid. For imperfectly matched hybrids, the melting temperature is reduced by approximately 1°C for each 1% mismatch.

The term "moderately stringent conditions" refers to conditions under which a DNA duplex with a greater degree of base pair mismatching than could occur under "highly stringent conditions" is able to form. Examples of typical "moderately stringent conditions" are 0.015M sodium chloride, 0.0015M sodium citrate at

50-65°C or 0.015M sodium chloride, 0.0015M sodium citrate, and 20% formamide at 37-50°C. By way of example, a "moderately stringent" condition of 50°C in 0.015 M sodium ion will allow about a 21% mismatch.

It will be appreciated by those skilled in the art that there is no absolute distinction between "highly" and "moderately" stringent conditions. For example, at 0.015M sodium ion (no formamide), the melting temperature of perfectly matched long DNA is about 71°C. With a wash at 65°C (at the same ionic strength), this would allow for approximately a 6% mismatch. To capture more distantly related sequences, one skilled in the art can simply lower the temperature or raise the ionic strength.

A good estimate of the melting temperature in 1M NaCl* for oligonucleotide probes up to about 20nt is given by:

$$T_m = 2°C \text{ per A-T base pair} + 4°C \text{ per G-C base pair}$$

*The sodium ion concentration in 6X salt sodium citrate (SSC) is 1M. See Suggs *et al.*, Developmental Biology Using Purified Genes, p. 683, Brown and Fox (eds.) (1981).

High stringency washing conditions for oligonucleotides are usually at a temperature of 0-5°C below the Tm of the oligonucleotide in 6X SSC, 0.1% SDS.

In another embodiment, related nucleic acid molecules comprise or consist of a nucleotide sequence that is about 70 percent identical to the nucleotide

sequence as shown in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, or comprise or consist essentially of a nucleotide sequence encoding a polypeptide that is about 70 percent identical to the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7. In preferred embodiments, the nucleotide sequences are about 75 percent, or about 80 percent, or about 85 percent, or about 90 percent, or about 95, 96, 97, 98, or 99 percent identical to the nucleotide sequence as shown in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, or the nucleotide sequences encode a polypeptide that is about 75 percent, or about 80 percent, or about 85 percent, or about 90 percent, or about 95, 96, 97, 98, or 99 percent identical to the polypeptide sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

Differences in the nucleic acid sequence may result in conservative and/or non-conservative modifications of the amino acid sequence relative to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

Conservative modifications to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 (and the corresponding modifications to the encoding nucleotides) will produce C3b/C4b CR-like polypeptides having functional and chemical characteristics similar to those of naturally occurring C3b/C4b CR-like polypeptide. In contrast, substantial modifications in the functional and/or chemical characteristics of C3b/C4b CR-like polypeptides may be accomplished by selecting substitutions in the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 that differ significantly in their effect on maintaining (a) the

structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for "alanine scanning mutagenesis."

Conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics, and other reversed or inverted forms of amino acid moieties.

Naturally occurring residues may be divided into classes based on common side chain properties:

1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;
2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
3) acidic: Asp, Glu;
4) basic: His, Lys, Arg;
5) residues that influence chain orientation: Gly, Pro; and
6) aromatic: Trp, Tyr, Phe.

For example, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted residues may be introduced into regions of the human C3b/C4b CR-like polypeptide that are homologous with non-human C3b/C4b CR-like polypeptide orthologs, or into the non-homologous regions of the molecule.

In making such changes, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics, these are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte *et al.*, *J. Mol. Biol.*, 157:105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those which are within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functionally equivalent protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. The greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, *i.e.*, with a biological property of the protein.

The following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). In making changes based upon similar hydrophilicity values, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those which are within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can

be used to identify important residues of the C3b/C4b CR-like polypeptide, or to increase or decrease the affinity of the C3b/C4b CR-like polypeptides described herein.

Exemplary amino acid substitutions are set forth in Table I.

Table I
Amino Acid Substitutions

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

A skilled artisan will be able to determine suitable variants of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 using well known techniques. For identifying suitable areas of the molecule that may be changed without destroying activity, one skilled in the art may target areas not believed to be important for activity. For example, when similar polypeptides with similar activities from the same species or from other species are known, one skilled in the art may compare the amino acid sequence of a C3b/C4b CR-like polypeptide to such similar polypeptides. With such a comparison, one can identify residues and portions of the molecules that are conserved among similar polypeptides. It will be appreciated that changes in areas of a C3b/C4b CR-like polypeptide that are not conserved relative to such similar polypeptides would be less likely to adversely affect the biological activity and/or structure of the C3b/C4b CR-like polypeptide. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids for the naturally occurring residues while retaining activity (conservative amino acid residue substitutions). Therefore, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a

C3b/C4b CR-like polypeptide that correspond to amino acid residues that are important for activity or structure in similar polypeptides. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues of C3b/C4b CR-like polypeptides.

One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of that information, one skilled in the art may predict the alignment of amino acid residues of a C3b/C4b CR-like polypeptide with respect to its three dimensional structure. One skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays know to those skilled in the art. Such variants could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change would be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., *Curr. Op. in Biotech.*, 7(4):422-427 (1996), Chou *et al.*, *Biochemistry*, 13(2):222-245 (1974); Chou *et al.*, *Biochemistry*, 113(2):211-222 (1974); Chou *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 47:45-148 (1978); Chou *et al.*, *Ann. Rev. Biochem.*, 47:251-276 and Chou *et al.*, *Biophys. J.*, 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural data base (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. *See* Holm *et al.*, *Nucl. Acid. Res.*, 27(1):244-247 (1999). It has been suggested (Brenner *et al.*, *Curr. Op. Struct. Biol.*, 7(3):369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will gain dramatically in accuracy.

Additional methods of predicting secondary structure include "threading" (Jones, D., *Curr. Opin. Struct. Biol.*, 7(3):377-87 (1997); Sippl *et al.*, *Structure*, 4(1):15-9 (1996)), "profile analysis" (Bowie *et al.*, *Science*, 253:164-170 (1991); Gribskov *et al.*, *Meth. Enzym.*, 183:146-159 (1990); Gribskov *et al.*,

Proc. Nat. Acad. Sci., 84(13):4355-4358 (1987)), and "evolutionary linkage" (See Home, *supra*, and Brenner, *supra*).

Preferred C3b/C4b CR-like polypeptide variants include glycosylation variants wherein the number and/or type of glycosylation sites has been altered compared to the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7. In one embodiment, C3b/C4b CR-like polypeptide variants comprise a greater or a lesser number of N-linked glycosylation sites than the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except prcline. The substitution(s) of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. Additional preferred C3b/C4b CR-like variants include cysteine variants, wherein one or more cysteine residues are deleted from or substituted for another amino acid (*e.g.*, serine) as compared to the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7. Cysteine variants are useful when C3b/C4b CR-like polypeptides must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion bodies. Cysteine

variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

In addition, the polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 or a C3b/C4b CR-like polypeptide variant may be fused to a homologous polypeptide to form a homodimer or to a heterologous polypeptide to form a heterodimer. Heterologous peptides and polypeptides include, but are not limited to: an epitope to allow for the detection and/or isolation of a C3b/C4b CR-like fusion polypeptide; a transmembrane receptor protein or a portion thereof, such as an extracellular domain, or a transmembrane and intracellular domain; a ligand or a portion thereof which binds to a transmembrane receptor protein; an enzyme or portion thereof which is catalytically active; a polypeptide or peptide which promotes oligomerization, such as a leucine zipper domain; a polypeptide or peptide which increases stability, such as an immunoglobulin constant region; and a polypeptide which has a therapeutic activity different from the polypeptide comprising the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or a C3b/C4b CR-like polypeptide variant.

Fusions can be made either at the amino terminus or at the carboxy terminus of the polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or a C3b/C4b CR-like polypeptide variant. Fusions may be direct with no linker or adapter molecule or indirect using a linker

or adapter molecule. A linker or adapter molecule may be one or more amino acid residues, typically up to about 20 to about 50 amino acid residues. A linker or adapter molecule may also be designed with a cleavage site for a DNA restriction endonuclease or for a protease to allow for the separation of the fused moieties. It will be appreciated that once constructed, the fusion polypeptides can be derivatized according to the methods described herein.

In a further embodiment of the invention, the polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or a C3b/C4b CR-like polypeptide variant is fused to one or more domains of an Fc region of human IgG. Antibodies comprise two functionally independent parts, a variable domain known as "Fab", which binds antigen, and a constant domain known as "Fc", which is involved in effector functions such as complement activation and attack by phagocytic cells. An Fc has a long serum half-life, whereas an Fab is short-lived. Capon *et al.*, *Nature*, 337:525-31 (1989). When constructed together with a therapeutic protein, an Fc domain can provide longer half-life or incorporate such functions as Fc receptor binding, protein A binding, complement fixation and perhaps even placental transfer. *Id.* Table II summarizes the use of certain Fc fusions known in the art.

TABLE II: FC FUSION WITH THERAPEUTIC PROTEINS

Form of Fc	**Fusion partner**	**Therapeutic implications**	**Reference**
IgG1	N-terminus of CD30-L	Hodgkin's disease; anaplastic lymphoma; T-cell leukemia	U.S. Patent No. 5,480,981
Murine Fcγ2a	IL-10	anti-inflammatory; transplant rejection	Zheng *et al.* (1995), *J. Immunol.*, 154: 5590-5600
IgG1	TNF receptor	septic shock	Fisher *et al.* (1996), *N. Engl. J. Med.*, 334: 1697-1702; Van Zee *et al.*, (1996), *J. Immunol.*, 156: 2221-2230
IgG, IgA, IgM, or IgE (excluding the first domain)	TNF receptor	inflammation, autoimmune disorders	U.S. Pat. No. 5,808,029, issued September 15, 1998
IgG1	CD4 receptor	AIDS	Capon *et al.* (1989), *Nature* 337: 525-531
IgG1, IgG3	N-terminus of IL-2	anti-cancer, antiviral	Harvill *et al.* (1995), *Immunotech.*, 1: 95-105
IgG1	C-terminus of OPG	osteoarthritis; bone density	WO 97/23614, published July 3, 1997
IgG1	N-terminus of leptin	anti-obesity	PCT/US 97/23183, filed December 11, 1997
Human Ig Cγ1	CTLA-4	autoimmune disorders	Linsley (1991), *J. Exp. Med.*, 174:561-569

In one example, all or a portion of the human IgG hinge, CH2 and CH3 regions may be fused at either the N-terminus or C-terminus of the C3b/C4b CR-like

polypeptides using methods known to the skilled artisan. The resulting C3b/C4b CR-like fusion polypeptide may be purified by use of a Protein A affinity column. Peptides and proteins fused to an Fc region have been found to exhibit a substantially greater half-life *in vivo* than the unfused counterpart. Also, a fusion to an Fc region allows for dimerization/multimerization of the fusion polypeptide. The Fc region may be a naturally occurring Fc region, or may be altered to improve certain qualities, such as therapeutic qualities, circulation time, reduce aggregation, etc.

Identity and similarity of related nucleic acid molecules and polypeptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York, 1991; and Carillo *et al.*, *SIAM J. Applied Math.*, 48:1073 (1988).

Preferred methods to determine identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are described in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, the GCG program package, including GAP (Devereux *et al.*, *Nucl. Acid. Res.*, 12:387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP,

BLASTN, and FASTA (Altschul *et al.*, *J. Mol. Biol.*, 215:403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (*BLAST Manual*, Altschul *et al.* NCB/NLM/NIH Bethesda, MD 20894; Altschul *et al.*, *supra*). The well known Smith Waterman algorithm may also be used to determine identity.

Certain alignment schemes for aligning two amino acid sequences may result in the matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full length sequences. Accordingly, in a preferred embodiment, the selected alignment method (GAP program) will result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

For example, using the computer algorithm GAP (Genetics Computer Group, University of Wisconsin, Madison, WI), two polypeptides for which the percent sequence identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3X the average diagonal; the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. A standard

comparison matrix (see Dayhoff *et al.*, Atlas of Protein Sequence and Structure, vol. 5, supp.3 (1978) for the PAM 250 comparison matrix; Henikoff *et al.*, *Proc. Natl. Acad. Sci* USA, 89:10915-10919 (1992) for the BLOSUM 62 comparison matrix) is also used by the algorithm.

Preferred parameters for a polypeptide sequence comparison include the following:

Algorithm: Needleman *et al.*, *J. Mol. Biol.*, 48:443-453 (1970);
Comparison matrix: BLOSUM 62 from Henikoff *et al.*, *Proc. Natl. Acad. Sci*. USA, 89:10915-10919 (1992);
Gap Penalty: 12
Gap Length Penalty: 4
Threshold of Similarity: 0

The GAP program is useful with the above parameters. The aforementioned parameters are the default parameters for polypeptide comparisons (along with no penalty for end gaps) using the GAP algorithm.

Preferred parameters for nucleic acid molecule sequence comparisons include the following:

Algorithm: Needleman *et al.*, *J. Mol Biol.*, 48:443-453 (1970);
Comparison matrix: matches = +10, mismatch = 0
Gap Penalty: 50
Gap Length Penalty: 3

The GAP program is also useful with the above parameters. The aforementioned parameters are the

default parameters for nucleic acid molecule comparisons.

Other exemplary algorithms, gap opening penalties, gap extension penalties, comparison matrices, thresholds of similarity, etc. may be used, including those set forth in the Program Manual, Wisconsin Package, Version 9, September, 1997. The particular choices to be made will be apparent to those of skill in the art and will depend on the specific comparison to be made, such as DNA to DNA, protein to protein, protein to DNA; and additionally, whether the comparison is between given pairs of sequences (in which case GAP or BestFit are generally preferred) or between one sequence and a large database of sequences (in which case FASTA or BLASTA are preferred).

Synthesis

It will be appreciated by those skilled in the art the nucleic acid and polypeptide molecules described herein may be produced by recombinant and other means.

Nucleic Acid Molecules

The nucleic acid molecules encode a polypeptide comprising the amino acid sequence of a C3b/C4b CR-like polypeptide can readily be obtained in a variety of ways including, without limitation, chemical synthesis, cDNA or genomic library screening, expression library screening and/or PCR amplification of cDNA.

Recombinant DNA methods used herein are generally those set forth in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory

Press, Cold Spring Harbor, NY (1989), and/or Ausubel *et al.*, eds., *Current Protocols in Molecular Biology*, Green Publishers Inc. and Wiley and Sons, NY (1994). The present invention provides for nucleic acid molecules as described herein and methods for obtaining the molecules.

Where a gene encoding the amino acid sequence of a C3b/C4b CR-like polypeptide has been identified from one species, all or a portion of that gene may be used as a probe to identify orthologs or related genes from the same species. The probes or primers may be used to screen cDNA libraries from various tissue sources believed to express the C3b/C4b CR-like polypeptide. In addition, part or all of a nucleic acid molecule having the sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6 may be used to screen a genomic library to identify and isolate a gene encoding the amino acid sequence of a C3b/C4b CR-like polypeptide. Typically, conditions of moderate or high stringency will be employed for screening to minimize the number of false positives obtained from the screen.

Nucleic acid molecules encoding the amino acid sequence of C3b/C4b CR-like polypeptides may also be identified by expression cloning which employs the detection of positive clones based upon a property of the expressed protein. Typically, nucleic acid libraries are screened by the binding of an antibody or other binding partner (*e.g.*, receptor or ligand) to cloned proteins which are expressed and displayed on a host cell surface. The antibody or binding partner is modified with a detectable label to identify those cells expressing the desired clone.

Recombinant expression techniques conducted in accordance with the descriptions set forth below may be followed to produce these polynucleotides and to express the encoded polypeptides. For example, by inserting a nucleic acid sequence which encodes the amino acid sequence of a C3b/C4b CR-like polypeptide into an appropriate vector, one skilled in the art can readily produce large quantities of the desired nucleotide sequence. The sequences can then be used to generate detection probes or amplification primers. Alternatively, a polynucleotide encoding the amino acid sequence of a C3b/C4b CR-like polypeptide can be inserted into an expression vector. By introducing the expression vector into an appropriate host, the encoded C3b/C4b CR-like polypeptide may be produced in large amounts.

Another method for obtaining a suitable nucleic acid sequence is the polymerase chain reaction (PCR). In this method, cDNA is prepared from poly(A)+RNA or total RNA using the enzyme reverse transcriptase. Two primers, typically complementary to two separate regions of cDNA (oligonucleotides) encoding the amino acid sequence of a C3b/C4b CR-like polypeptide, are then added to the cDNA along with a polymerase such as *Taq* polymerase, and the polymerase amplifies the cDNA region between the two primers.

Another means of preparing a nucleic acid molecule encoding the amino acid sequence of a C3b/C4b CR-like polypeptide is chemical synthesis using methods well known to the skilled artisan such as those described by Engels *et al.*, *Angew. Chem. Intl. Ed.*, 28:716-734 (1989). These methods include, *inter alia*, the

phosphotriester, phosphoramidite, and H-phosphonate methods for nucleic acid synthesis. A preferred method for such chemical synthesis is polymer-supported synthesis using standard phosphoramidite chemistry. Typically, the DNA encoding the amino acid sequence of a C3b/C4b CR-like polypeptide will be several hundred nucleotides in length. Nucleic acids larger than about 100 nucleotides can be synthesized as several fragments using these methods. The fragments can then be ligated together to form the full length nucleotide sequence of a C3b/C4b CR-like polypeptide. Usually, the DNA fragment encoding the amino terminus of the polypeptide will have an ATG, which encodes a methionine residue. This methionine may or may not be present on the mature form of the C3b/C4b CR-like polypeptide, depending on whether the polypeptide produced in the host cell is designed to be secreted from that cell. Other methods known to the skilled artisan may be used as well.

In certain embodiments, nucleic acid variants contain codons which have been altered for the optimal expression of a C3b/C4b CR-like polypeptide in a given host cell. Particular codon alterations will depend upon the C3b/C4b CR-like polypeptide(s) and host cell(s) selected for expression. Such "codon optimization" can be carried out by a variety of methods, for example, by selecting codons which are preferred for use in highly expressed genes in a given host cell. Computer algorithms which incorporate codon frequency tables such as "Ecohigh.cod" for codon preference of highly expressed bacterial genes may be used and are provided by the University of Wisconsin Package Version 9.0, Genetics Computer Group, Madison, WI. Other useful codon frequency tables include

"Celegans_high.cod", "Celegans_low.cod", "Drosophila_high.cod", "Human_high.cod", "Maize_high.cod", and "Yeast_high.cod".

Vectors and Host Cells

A nucleic acid molecule encoding the amino acid sequence of a C3b/C4b CR-like polypeptide may be inserted into an appropriate expression vector using standard ligation techniques. The vector is typically selected to be functional in the particular host cell employed (*i.e.*, the vector is compatible with the host cell machinery such that amplification of the gene and/or expression of the gene can occur). A nucleic acid molecule encoding the amino acid sequence of a C3b/C4b CR-like polypeptide may be amplified/expressed in prokaryotic, yeast, insect (baculovirus systems), and/or eukaryotic host cells. Selection of the host cell will depend in part on whether a C3b/C4b CR-like polypeptide is to be post-translationally modified (*e.g.*, glycosylated and/or phosphorylated). If so, yeast, insect, or mammalian host cells are preferable. For a review of expression vectors, see *Meth. Enz.*, v.185, D.V. Goeddel, ed. Academic Press Inc., San Diego, CA (1990).

Typically, expression vectors used in any of the host cells will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron

sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

Optionally, the vector may contain a "tag"-encoding sequence, *i.e.*, an oligonucleotide molecule located at the 5' or 3' end of the C3b/C4b CR-like polypeptide coding sequence; the oligonucleotide sequence encodes polyHis (such as hexaHis), or other "tag" such as FLAG, HA (hemaglutinin Influenza virus) or *myc* for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification of the C3b/C4b CR-like polypeptide from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified C3b/C4b CR-like polypeptide by various means such as using certain peptidases for cleavage.

Flanking sequences may be homologous (*i.e.*, from the same species and/or strain as the host cell), heterologous (*i.e.*, from a species other than the host cell species or strain), hybrid (*i.e.*, a combination of flanking sequences from more than one source) or synthetic, or the flanking sequences may be native sequences which normally function to regulate C3b/C4b CR-like polypeptide expression. As such, the source of

a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

The flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein other than the C3b/C4b CR-like gene flanking sequences will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described herein for nucleic acid synthesis or cloning.

Where all or only a portion of the flanking sequence is known, it may be obtained using PCR and/or by screening a genomic library with suitable oligonucleotide and/or flanking sequence fragments from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen® column chromatography (Chatsworth, CA), or other methods known to the skilled artisan. The selection of suitable

enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. Amplification of the vector to a certain copy number can, in some cases, be important for the optimal expression of a C3b/C4b CR-like polypeptide. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (Product No. 303-3s, New England Biolabs, Beverly, MA) is suitable for most Gram-negative bacteria and various origins (*e.g.*, SV40, polyoma, adenovirus, vesicular stomatitus virus (VSV) or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it contains the early promoter).

A transcription termination sequence is typically located 3' of the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

A selectable marker gene element encodes a protein necessary for the survival and growth of a host cell

grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, tetracycline, or kanamycin for prokaryotic host cells, (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex media. Preferred selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. A neomycin resistance gene may also be used for selection in prokaryotic and eukaryotic host cells.

Other selection genes may be used to amplify the gene which will be expressed. Amplification is the process wherein genes which are in greater demand for the production of a protein critical for growth are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and thymidine kinase. The mammalian cell transformants are placed under selection pressure which only the transformants are uniquely adapted to survive by virtue of the selection gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively changed, thereby leading to the amplification of both the selection gene and the DNA that encodes a C3b/C4b CR-like polypeptide. As a result, increased quantities of C3b/C4b CR-like polypeptide are synthesized from the amplified DNA.

A ribosome binding site is usually necessary for translation initiation of mRNA and is characterized by

a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of a C3b/C4b CR-like polypeptide to be expressed. The Shine-Dalgarno sequence is varied but is typically a polypurine (*i.e.*, having a high A-G content). Many Shine-Dalgarno sequences have been identified, each of which can be readily synthesized using methods set forth herein and used in a prokaryotic vector.

A leader, or signal, sequence may be used to direct a C3b/C4b CR-like polypeptide out of the host cell. Typically, a nucleotide sequence encoding the signal sequence is positioned in the coding region of a C3b/C4b CR-like nucleic acid molecule, or directly at the 5' end of a C3b/C4b CR-like polypeptide coding region. Many signal sequences have been identified, and any of those that are functional in the selected host cell may be used in conjunction with a C3b/C4b CR-like nucleic acid molecule. Therefore, a signal sequence may be homologous (naturally occurring) or heterologous to a C3b/C4b CR-like gene or cDNA. Additionally, a signal sequence may be chemically synthesized using methods described herein. In most cases, the secretion of a C3b/C4b CR-like polypeptide from the host cell via the presence of a signal peptide will result in the removal of the signal peptide from the secreted C3b/C4b CR-like polypeptide. The signal sequence may be a component of the vector, or it may be a part of a C3b/C4b CR-like nucleic acid molecule that is inserted into the vector.

Included within the scope of this invention is the use of either a nucleotide sequence encoding a native

C3b/C4b CR-like polypeptide signal sequence joined to a C3b/C4b CR-like polypeptide coding region or a nucleotide sequence encoding a heterologous signal sequence joined to a C3b/C4b CR-like polypeptide coding region. The heterologous signal sequence selected should be one that is recognized and processed, *i.e.*, cleaved by a signal peptidase, by the host cell. For prokaryotic host cells that do not recognize and process the native C3B/C4B CR-like polypeptide signal sequence, the signal sequence is substituted by a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, or heat-stable enterotoxin II leaders. For yeast secretion, the native C3B/C4B CR-like polypeptide signal sequence may be substituted by the yeast invertase, alpha factor, or acid phosphatase leaders. In mammalian cell expression the native signal sequence is satisfactory, although other mammalian signal sequences may be suitable.

In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one may manipulate the various presequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add presequences, which also may affect glycosylation. The final protein product may have, in the -1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the N-terminus. Alternatively, use of some enzyme cleavage sites may

result in a slightly truncated form of the desired C3b/C4b CR-like polypeptide, if the enzyme cuts at such area within the mature polypeptide.

In many cases, transcription of a nucleic acid molecule is increased by the presence of one or more introns in the vector; this is particularly true where a polypeptide is produced in eukaryotic host cells, especially mammalian host cells. The introns used may be naturally occurring within the C3b/C4b CR-like gene, especially where the gene used is a full length genomic sequence or a fragment thereof. Where the intron is not naturally occurring within the gene (as for most cDNAs), the intron(s) may be obtained from another source. The position of the intron with respect to flanking sequences and the C3b/C4b CR-like gene is generally important, as the intron must be transcribed to be effective. Thus, when a C3b/C4b CR-like cDNA molecule is being transcribed, the preferred position for the intron is 3' to the transcription start site, and 5' to the polyA transcription termination sequence. Preferably, the intron or introns will be located on one side or the other (*i.e.*, 5' or 3') of the cDNA such that it does not interrupt the coding sequence. Any intron from any source, including any viral, prokaryotic and eukaryotic (plant or animal) organisms, may be used to practice this invention, provided that it is compatible with the host cell(s) into which it is inserted. Also included herein are synthetic introns. Optionally, more than one intron may be used in the vector.

The expression and cloning vectors of the present invention will each typically contain a promoter that is recognized by the host organism and operably linked

to the molecule encoding a C3B/C4B CR-like polypeptide. Promoters are untranscribed sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription of the structural gene. Promoters are conventionally grouped into one of two classes, inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, initiate continual gene product production; that is, there is little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding a C3B/C4B CR-like polypeptide by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector. The native C3B/C4B CR-like gene promoter sequence may be used to direct amplification and/or expression of a C3B/C4B CR-like nucleic acid molecule. A heterologous promoter is preferred, however, if it permits greater transcription and higher yields of the expressed protein as compared to the native promoter, and if it is compatible with the host cell system that has been selected for use.

Promoters suitable for use with prokaryotic hosts include the beta-lactamase and lactose promoter systems; alkaline phosphatase, a tryptophan (trp) promoter system; and hybrid promoters such as the tac promoter. Other known bacterial promoters are also

suitable. Their sequences have been published, thereby enabling one skilled in the art to ligate them to the desired DNA sequence(s), using linkers or adapters as needed to supply any useful restriction sites.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus (CMV), a retrovirus, hepatitis-B virus and most preferably Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, *e.g.*, heat-shock promoters and the actin promoter.

Additional promoters which may be of interest in controlling C3B/C4B CR-like gene transcription include, but are not limited to: the SV40 early promoter region (Bernoist and Chambon, *Nature*, 290:304-310, 1981); the CMV promoter; the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, *Cell*, 22:787-797, 1980); the herpes thymidine kinase promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. USA*, 78:144-1445, 1981); the regulatory sequences of the metallothionine gene (Brinster *et al.*, *Nature*, 296:39-42, 1982); prokaryotic expression vectors such as the beta-lactamase promoter (Villa-Kamaroff, *et al.*, *Proc. Natl. Acad. Sci. USA*, 75:3727-3731, 1978); or the tac promoter (DeBoer, *et al.*, *Proc. Natl. Acad. Sci. USA*, 80:21-25, 1983). Also of interest are the following

animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, *Cell*, 38:639-646, 1984; Ornitz *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, 50:399-409 (1986); MacDonald, *Hepatology*, 7:425-515, 1987); the insulin gene control region which is active in pancreatic beta cells (Hanahan, *Nature*, 315:115-122, 1985); the immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, *Cell*, 38:647-658 (1984); Adames *et al.*, *Nature*, 318:533-538 (1985); Alexander *et al.*, *Mol. Cell. Biol.*, 7:1436-1444, 1987); the mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, *Cell*, 45:485-495, 1986); the albumin gene control region which is active in liver (Pinkert *et al.*, *Genes and Devel.*, 1:268-276, 1987); the alphafetoprotein gene control region which is active in liver (Krumlauf *et al.*, *Mol. Cell. Biol.*, 5:1639-1648, 1985; Hammer *et al.*, *Science*, 235:53-58, 1987); the alpha 1-antitrypsin gene control region which is active in the liver (Kelsey *et al.*, *Genes and Devel.*, 1:161-171, 1987); the beta-globin gene control region which is active in myeloid cells (Mogram *et al.*, *Nature*, 315:338-340, 1985; Kollias *et al.*, *Cell*, 46:89-94, 1986); the myelin basic protein gene control region which is active in oligodendrocyte cells in the brain (Readhead *et al.*, *Cell*, 48:703-712, 1987); the myosin light chain-2 gene control region which is active in skeletal muscle (Sani, *Nature*, 314:283-286, 1985); and the gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason *et al.*,

Science, 234:1372-1378, 1986).

An enhancer sequence may be inserted into the vector to increase the transcription of a DNA encoding a C3B/C4B CR-like polypeptide of the present invention by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent. They have been found 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (*e.g.*, globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus will be used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be spliced into the vector at a position 5′ or 3′ to a C3B/C4B CR-like nucleic acid molecule, it is typically located at a site 5' from the promoter.

Expression vectors of the invention may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired flanking sequences. Where one or more of the desired flanking sequences are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art.

Preferred vectors for practicing this invention are those which are compatible with bacterial, insect, and mammalian host cells. Such vectors include, *inter*

alia, pCRII, pCR3, and pcDNA3.1 (Invitrogen Company, Carlsbad, CA), pBSII (Stratagene Company, La Jolla, CA), pET15□ (Novagen, Madison, WI), pGEX (Pharmacia Biotech, Piscataway, NJ), pEGFP-N2 (Clontech, Palo Alto, CA), pETL (BlueBacII; Invitrogen), pDSR-alpha (PCT Publication No. WO90/14363) and pFastBacDual (Gibco/BRL, Grand Island, NY).

Additional suitable vectors include, but are not limited to, cosmids, plasmids or modified viruses, but it will be appreciated that the vector system must be compatible with the selected host cell. Such vectors include, but are not limited to plasmids such as Bluescript® plasmid derivatives (a high copy number ColE1-based phagemid, Stratagene Cloning Systems Inc., La Jolla CA), PCR cloning plasmids designed for cloning Taq-amplified PCR products (*e.g.*, TOPO™ TA Cloning® Kit, PCR2.1® plasmid derivatives, Invitrogen, Carlsbad, CA), and mammalian, yeast, or virus vectors such as a baculovirus expression system (pBacPAK plasmid derivatives, Clontech, Palo Alto, CA).

After the vector has been constructed and a nucleic acid molecule encoding a C3b/C4b CR-like polypeptide has been inserted into the proper site of the vector, the completed vector may be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector for a C3b/C4b CR-like polypeptide into a selected host cell may be accomplished by well known methods including methods such as transfection, infection, calcium chloride, electroporation, microinjection, lipofection or the DEAE-dextran method or other known techniques. The method selected will in part be a

function of the type of host cell to be used. These methods and other suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook *et al.*, *supra*.

Host cells may be prokaryotic host cells (such as *E. coli*) or eukaryotic host cells (such as a yeast cell, an insect cell or a vertebrate cell). The host cell, when cultured under appropriate conditions, synthesizes a C3b/C4b CR-like polypeptide which can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity, such as glycosylation or phosphorylation, and ease of folding into a biologically active molecule.

A number of suitable host cells are known in the art and many are available from the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209. Examples include, but are not limited to, mammalian cells, such as Chinese hamster ovary cells (CHO) (ATCC No. CCL61) CHO DHFR- cells (Urlaub *et al.*, *Proc. Natl. Acad. Sci. USA*, 97:4216-4220 (1980)), human embryonic kidney (HEK) 293 or 293T cells (ATCC No. CRL1573), or 3T3 cells (ATCC No. CCL92). The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. Other suitable mammalian cell lines, are the monkey COS-1 (ATCC No. CRL1650) and COS-7 cell lines (ATCC No. CRL1651), and

the CV-1 cell line (ATCC No. CCL70). Further exemplary mammalian host cells include primate cell lines and rodent cell lines, including transformed cell lines. Normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, as well as primary explants, are also suitable. Candidate cells may be genotypically deficient in the selection gene, or may contain a dominantly acting selection gene. Other suitable mammalian cell lines include but are not limited to, mouse neuroblastoma N2A cells, HeLa, mouse L-929 cells, 3T3 lines derived from Swiss, Balb-c or NIH mice, BHK or HaK hamster cell lines, which are available from the ATCC. Each of these cell lines is known by and available to those skilled in the art of protein expression.

Similarly useful as host cells suitable for the present invention are bacterial cells. For example, the various strains of *E. coli* (*e.g.*, HB101, (ATCC No. 33694) DH5α, DH10, and MC1061 (ATCC No. 53338)) are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Pseudomonas spp.*, other *Bacillus spp.*, *Streptomyces spp.*, and the like may also be employed in this method.

Many strains of yeast cells known to those skilled in the art are also available as host cells for the expression of the polypeptides of the present invention. Preferred yeast cells include, for example, *Saccharomyces cerivisae* and *Pichia pastoris*.

Additionally, where desired, insect cell systems may be utilized in the methods of the present invention. Such systems are described for example in Kitts *et al.*, *Biotechniques*, 14:810-817 (1993);

Lucklow, *Curr. Opin. Biotechnol.*, 4:564-572 (1993); and Lucklow *et al.* (*J. Virol.*, 67:4566-4579 (1993). Preferred insect cells are Sf-9 and Hi5 (Invitrogen, Carlsbad, CA).

One may also use transgenic animals to express glycosylated C3b/C4b CR-like polypeptides. For example, one may use a transgenic milk-producing animal (a cow or goat, for example) and obtain the present glycosylated polypeptide in the animal milk. One may also use plants to produce C3b/C4b CR-like polypeptides, however, in general, the glycosylation occurring in plants is different from that produced in mammalian cells, and may result in a glycosylated product which is not suitable for human therapeutic use.

Polypeptide Production

Host cells comprising a C3b/C4b CR-like polypeptide expression vector may be cultured using standard media well known to the skilled artisan. The media will usually contain all nutrients necessary for the growth and survival of the cells. Suitable media for culturing *E. coli* cells include, for example, Luria Broth (LB) and/or Terrific Broth (TB). Suitable media for culturing eukaryotic cells include Roswell Park Memorial Institute medium 1640 (RPMI 1640), Minimal Essential Medium (MEM) and/or Dulbecco's Modified Eagle Medium (DMEM), all of which may be supplemented with serum and/or growth factors as indicated by the particular cell line being cultured. A suitable medium for insect cultures is Grace's medium supplemented with

yeastolate, lactalbumin hydrolysate and/or fetal calf serum, as necessary.

Typically, an antibiotic or other compound useful for selective growth of transformed cells is added as a supplement to the media. The compound to be used will be dictated by the selectable marker element present on the plasmid with which the host cell was transformed. For example, where the selectable marker element is kanamycin resistance, the compound added to the culture medium will be kanamycin. Other compounds for selective growth include ampicillin, tetracycline, and neomycin.

The amount of a C3b/C4b CR-like polypeptide produced by a host cell can be evaluated using standard methods known in the art. Such methods include, without limitation, Western blot analysis, SDS-polyacrylamide gel electrophoresis, non-denaturing gel electrophoresis, HPLC separation, immunoprecipitation, and/or activity assays such as DNA binding gel shift assays.

If a C3b/C4b CR-like polypeptide has been designed to be secreted from the host cells, the majority of polypeptide may be found in the cell culture medium. If however, the C3b/C4b CR-like polypeptide is not secreted from the host cells, it will be present in the cytoplasm and/or the nucleus (for eukaryotic host cells) or in the cytosol (for bacterial host cells).

For a C3b/C4b CR-like polypeptide situated in the host cell cytoplasm and/or the nucleus (for eukaryotic host cells) or in the cytosol (for bacterial host cells), intracellular material (including inclusion

bodies for gram-negative bacteria) can be extracted from the host cell using any standard technique known to the skilled artisan. For example, the host cells can be lysed to release the contents of the periplasm/cytoplasm by French press, homogenization, and/or sonication followed by centrifugation.

If a C3b/C4b CR-like polypeptide has formed inclusion bodies in the cytosol, the inclusion bodies can often bind to the inner and/or outer cellular membranes and thus will be found primarily in the pellet material after centrifugation. The pellet material can then be treated at pH extremes or with a chaotropic agent such as a detergent, guanidine, guanidine derivatives, urea, or urea derivatives in the presence of a reducing agent such as dithiothreitol at alkaline pH or tris carboxyethyl phosphine at acid pH to release, break apart, and solubilize the inclusion bodies. The C3b/C4b CR-like polypeptide in its now soluble form can then be analyzed using gel electrophoresis, immunoprecipitation or the like. If it is desired to isolate the C3b/C4b CR-like polypeptide, isolation may be accomplished using standard methods such as those described herein and in Marston *et al.*, *Meth. Enz.*, 182:264-275 (1990).

In some cases, a C3b/C4b CR-like polypeptide may not be biologically active upon isolation. Various methods for "refolding" or converting the polypeptide to its tertiary structure and generating disulfide linkages can be used to restore biological activity. Such methods include exposing the solubilized polypeptide to a pH usually above 7 and in the presence of a particular concentration of a chaotrope. The selection of chaotrope is very similar to the choices

used for inclusion body solubilization, but usually the chaotrope is used at a lower concentration and is not necessarily the same as chaotropes used for the solubilization. In most cases the refolding/oxidation solution will also contain a reducing agent or the reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential allowing for disulfide shuffling to occur in the formation of the protein's cysteine bridge(s). Some of the commonly used redox couples include cysteine/cystamine, glutathione (GSH)/dithiobis GSH, cupric chloride, dithiothreitol(DTT)/ dithiane DTT, and 2-2mercaptoethanol(bME)/dithio-b(ME). A cosolvent may be used to increase the efficiency of the refolding, and the more common reagents used for this purpose include glycerol, polyethylene glycol of various molecular weights, arginine and the like.

If inclusion bodies are not formed to a significant degree upon expression of a C3b/C4b CR-like polypeptide, then the polypeptide will be found primarily in the supernatant after centrifugation of the cell homogenate. The polypeptide may be further isolated from the supernatant using methods such as those described herein.

The purification of a C3b/C4b CR-like polypeptide from solution can be accomplished using a variety of techniques. If the polypeptide has been synthesized such that it contains a tag such as Hexahistidine (C3b/C4b CR-like polypeptide/hexaHis) or other small peptide such as FLAG (Eastman Kodak Co., New Haven, CT) or *myc* (Invitrogen, Carlsbad, CA) at either its carboxyl or amino terminus, it may be purified in a one-step process by passing the solution through an

affinity column where the column matrix has a high affinity for the tag.

For example, polyhistidine binds with great affinity and specificity to nickel, thus an affinity column of nickel (such as the Qiagen® nickel columns) can be used for purification of C3b/C4b CR-like polypeptide/polyHis. See for example, Ausubel *et al.*, eds., *Current Protocols in Molecular Biology*, Section 10.11.8, John Wiley & Sons, New York (1993).

Additionally, the C3B/C4B CR-like polypeptide may be purified through the use of a monoclonal antibody which is capable of specifically recognizing and binding to the C3B/C4B CR-like polypeptide.

Suitable procedures for purification thus include, without limitation, affinity chromatography, immunoaffinity chromatography, ion exchange chromatography, molecular sieve chromatography, High Performance Liquid Chromatography (HPLC), electrophoresis (including native gel electrophoresis) followed by gel elution, and preparative isoelectric focusing ("Isoprime" machine/technique, Hoefer Scientific, San Francisco, CA). In some cases, two or more purification techniques may be combined to achieve increased purity.

C3b/C4b CR-like polypeptides may also be prepared by chemical synthesis methods (such as solid phase peptide synthesis) using techniques known in the art, such as those set forth by Merrifield *et al.*, *J. Am. Chem. Soc.*, 85:2149 (1963), Houghten *et al.*, *Proc Natl Acad. Sci. USA*, 82:5132 (1985), and Stewart and Young, Solid Phase Peptide Synthesis, Pierce Chemical Co.,

Rockford, IL (1984). Such polypeptides may be synthesized with or without a methionine on the amino terminus. Chemically synthesized C3b/C4b CR-like polypeptides may be oxidized using methods set forth in these references to form disulfide bridges. Chemically synthesized C3b/C4b CR-like polypeptides are expected to have comparable biological activity to the corresponding C3b/C4b CR-like polypeptides produced recombinantly or purified from natural sources, and thus may be used interchangeably with a recombinant or natural C3b/C4b CR-like polypeptide.

Another means of obtaining a C3b/C4b CR-like polypeptide is via purification from biological samples such as source tissues and/or fluids in which the C3b/C4b CR-like polypeptide is naturally found. Such purification can be conducted using methods for protein purification as described herein. The presence of the C3b/C4b CR-like polypeptide during purification may be monitored using, for example, an antibody prepared against recombinantly produced C3b/C4b CR-like polypeptide or peptide fragments thereof.

A number of additional methods for producing nucleic acids and polypeptides are known in the art, and can be used to produce polypeptides having specificity for C3b/C4b CR-like. See for example, Roberts *et al.*, *Proc. Natl. Acad. Sci.*, 94:12297-12303 (1997), which describes the production of fusion proteins between an mRNA and its encoded peptide. *See also* Roberts, R., *Curr. Opin. Chem. Biol.*, 3:268-273 (1999). Additionally, U.S. patent No. 5,824,469 describes methods of obtaining oligonucleotides capable of carrying out a specific biological function. The

procedure involves generating a heterogeneous pool of oligonucleotides, each having a 5′ randomized sequence, a central preselected sequence, and a 3′ randomized sequence. The resulting heterogeneous pool is introduced into a population of cells that do not exhibit the desired biological function. Subpopulations of the cells are then screened for those which exhibit a predetermined biological function. From that subpopulation, oligonucleotides capable of carrying out the desired biological function are isolated.

U.S. Patent Nos. 5,763,192, 5,814,476, 5,723,323, and 5,817,483 describe processes for producing peptides or polypeptides. This is done by producing stochastic genes or fragments thereof, and then introducing these genes into host cells which produce one or more proteins encoded by the stochastic genes. The host cells are then screened to identify those clones producing peptides or polypeptides having the desired activity.

Chemical Derivatives

Chemically modified derivatives of the C3b/C4b CR-like polypeptides may be prepared by one skilled in the art, given the disclosures set forth hereinbelow. C3b/C4b CR-like polypeptide derivatives are modified in a manner that is different, either in the type or location of the molecules naturally attached to the polypeptide. Derivatives may include molecules formed by the deletion of one or more naturally-attached chemical groups. The polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID

NO:7, or a C3b/C4b CR-like polypeptide variant may be modified by the covalent attachment of one or more polymers. For example, the polymer selected is typically water soluble so that the protein to which it is attached does not precipitate in an aqueous environment, such as a physiological environment. Included within the scope of suitable polymers is a mixture of polymers. Preferably, for therapeutic use of the end-product preparation, the polymer will be pharmaceutically acceptable.

The polymers each may be of any molecular weight and may be branched or unbranched. The polymers each typically have an average molecular weight of between about 2kDa to about 100kDa (the term "about" indicating that in preparations of a water soluble polymer, some molecules will weigh more, some less, than the stated molecular weight). The average molecular weight of each polymer preferably is between about 5kDa and about 50kDa, more preferably between about 12kDa and about 40kDa and most preferably between about 20kDa and about 35kDa.

Suitable water soluble polymers or mixtures thereof include, but are not limited to, N-linked or O-linked carbohydrates, sugars, phosphates, polyethylene glycol (PEG) (including the forms of PEG that have been used to derivatize proteins, including mono-(C_1-C_{10}) alkoxy- or aryloxy-polyethylene glycol), monomethoxy-polyethylene glycol, dextran (such as low molecular weight dextran, of, for example about 6 kD), cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-

polymer, polyoxyethylated polyols (*e.g.*, glycerol) and polyvinyl alcohol. Also encompassed by the present invention are bifunctional crosslinking molecules which may be used to prepare covalently attached multimers of the polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or a C3b/C4b CR-like polypeptide variant.

In general, chemical derivatization may be performed under any suitable condition used to react a protein with an activated polymer molecule. Methods for preparing chemical derivatives of polypeptides will generally comprise the steps of (a) reacting the polypeptide with the activated polymer molecule (such as a reactive ester or aldehyde derivative of the polymer molecule) under conditions whereby the polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or a C3b/C4b CR-like polypeptide variant becomes attached to one or more polymer molecules, and (b) obtaining the reaction product(s). The optimal reaction conditions will be determined based on known parameters and the desired result. For example, the larger the ratio of polymer molecules:protein, the greater the percentage of attached polymer molecule. In one embodiment, the C3b/C4b CR-like polypeptide derivative may have a single polymer molecule moiety at the amino terminus. See, for example, U.S. Patent No. 5,234,784.

The pegylation of the polypeptide specifically may be carried out by any of the pegylation reactions known in the art, as described for example in the following references: Francis *et al.*, *Focus on Growth Factors*, 3:4-10 (1992); EP 0154316; EP 0401384 and U.S. Patent

No. 4,179,337. For example, pegylation may be carried out via an acylation reaction or an alkylation reaction with a reactive polyethylene glycol molecule (or an analogous reactive water-soluble polymer) as described herein. For the acylation reactions, the polymer(s) selected should have a single reactive ester group. For reductive alkylation, the polymer(s) selected should have a single reactive aldehyde group. A reactive aldehyde is, for example, polyethylene glycol propionaldehyde, which is water stable, or mono C_1-C_{10} alkoxy or aryloxy derivatives thereof (see U.S. Patent No. 5,252,714).

In another embodiment, C3b/C4b CR-like polypeptides may be chemically coupled to biotin, and the biotin/C3b/C4b CR-like polypeptide molecules which are conjugated are then allowed to bind to avidin, resulting in tetravalent avidin/biotin/C3b/C4b CR-like polypeptide molecules. C3b/C4b CR-like polypeptides may also be covalently coupled to dinitrophenol (DNP) or trinitrophenol (TNP) and the resulting conjugates precipitated with anti-DNP or anti-TNP-IgM to form decameric conjugates with a valency of 10.

Generally, conditions which may be alleviated or modulated by the administration of the present C3b/C4b CR-like polypeptide derivatives include those described herein for C3b/C4b CR-like polypeptides. However, the C3b/C4b CR-like polypeptide derivatives disclosed herein may have additional activities, enhanced or reduced biological activity, or other characteristics, such as increased or decreased half-life, as compared to the non-derivatized molecules.

Genetically Engineered Non-Human Animals

Additionally included within the scope of the present invention are non-human animals such as mice, rats, or other rodents, rabbits, goats, or sheep, or other farm animals, in which the gene (or genes) encoding the native C3b/C4b CR-like polypeptide has (have) been disrupted ("knocked out") such that the level of expression of this gene or genes is (are) significantly decreased or completely abolished. Such animals may be prepared using techniques and methods such as those described in U.S. Patent No. 5,557,032.

The present invention further includes non-human animals such as mice, rats, or other rodents, rabbits, goats, sheep, or other farm animals, in which either the native form of the C3b/C4b CR-like gene(s) for that animal or a heterologous C3b/C4b CR-like gene(s) is (are) over-expressed by the animal, thereby creating a "transgenic" animal. Such transgenic animals may be prepared using well known methods such as those described in U.S. Patent No 5,489,743 and PCT application No. WO94/28122.

The present invention further includes non-human animals in which the promoter for one or more of the C3b/C4b CR-like polypeptides of the present invention is either activated or inactivated (*e.g.*, by using homologous recombination methods) to alter the level of expression of one or more of the native C3b/C4b CR-like polypeptides.

These non-human animals may be used for drug candidate screening. In such screening, the impact of a drug candidate on the animal may be measured. For

example, drug candidates may decrease or increase the expression of the C3b/C4b CR-like gene. In certain embodiments, the amount of C3b/C4b CR-like polypeptide, that is produced may be measured after the exposure of the animal to the drug candidate. Additionally, in certain embodiments, one may detect the actual impact of the drug candidate on the animal. For example, the overexpression of a particular gene may result in, or be associated with, a disease or pathological condition. In such cases, one may test a drug candidate's ability to decrease expression of the gene or its ability to prevent or inhibit a pathological condition. In other examples, the production of a particular metabolic product such as a fragment of a polypeptide, may result in, or be associated with, a disease or pathological condition. In such cases, one may test a drug candidate's ability to decrease the production of such a metabolic product or its ability to prevent or inhibit a pathological condition.

Microarray

It will be appreciated that DNA microarray technology can be utilized in accordance with the present invention. DNA microarrays are miniature, high density arrays of nucleic acids positioned on a solid support, such as glass. Each cell or element within the array has numerous copies of a single species of DNA which acts as a target for hybridization for its cognate mRNA. In expression profiling using DNA microarray technology, mRNA is first extracted from a cell or tissue sample and then converted enzymatically to fluorescently labeled cDNA. This material is hybridized to the microarray and unbound cDNA is

removed by washing. The expression of discrete genes represented on the array is then visualized by quantitating the amount of labeled cDNA which is specifically bound to each target DNA. In this way, the expression of thousands of genes can be quantitated in a high throughput, parallel manner from a single sample of biological material.

This high throughput expression profiling has a broad range of applications with respect to the C3b/C4b CR-like molecules of the invention, including, but not limited to: the identification and validation of C3b/C4b CR-like disease-related genes as targets for therapeutics; molecular toxicology of C3b/C4b CR-like molecules and inhibitors thereof; stratification of populations and generation of surrogate markers for clinical trials; and enhancing C3b/C4b CR-like-related small molecule drug discovery by aiding in the identification of selective compounds in high throughput screens (HTS).

Selective Binding Agents

As used herein, the term "selective binding agent" refers to a molecule which has specificity for one or more C3b/C4b CR-like polypeptides. Suitable selective binding agents include, but are not limited to, antibodies and derivatives thereof, polypeptides, and small molecules. Suitable selective binding agents may be prepared using methods known in the art. An exemplary C3B/C4B CR-like polypeptide selective binding agent of the present invention is capable of binding a certain portion of the C3B/C4B CR-like polypeptide

thereby inhibiting the binding of the polypeptide to the C3B/C4B CR-like polypeptide receptor(s).

Selective binding agents such as antibodies and antibody fragments that bind C3b/C4b CR-like polypeptides are within the scope of the present invention. The antibodies may be polyclonal including monospecific polyclonal, monoclonal (MAbs), recombinant, chimeric, humanized such as CDR-grafted, human, single chain, and/or bispecific, as well as fragments, variants or derivatives thereof. Antibody fragments include those portions of the antibody which bind to an epitope on the C3B/C4B CR-like polypeptide. Examples of such fragments include Fab and F(ab') fragments generated by enzymatic cleavage of full-length antibodies. Other binding fragments include those generated by recombinant DNA techniques, such as the expression of recombinant plasmids containing nucleic acid sequences encoding antibody variable regions.

Polyclonal antibodies directed toward a C3b/C4b CR-like polypeptide generally are produced in animals (*e.g.*, rabbits or mice) by means of multiple subcutaneous or intraperitoneal injections of C3b/C4b CR-like polypeptide and an adjuvant. It may be useful to conjugate a C3b/C4b CR-like polypeptide to a carrier protein that is immunogenic in the species to be immunized, such as keyhole limpet heocyanin, serum, albumin, bovine thyroglobulin, or soybean trypsin inhibitor. Also, aggregating agents such as alum are used to enhance the immune response. After immunization, the animals are bled and the serum is

assayed for anti-C3b/C4b CR-like polypeptide antibody titer.

Monoclonal antibodies directed toward a C3b/C4b CR-like polypeptide are produced using any method which provides for the production of antibody molecules by continuous cell lines in culture. Examples of suitable methods for preparing monoclonal antibodies include the hybridoma methods of Kohler *et al.*, *Nature*, 256:495-497 (1975) and the human B-cell hybridoma method, Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987). Also provided by the invention are hybridoma cell lines which produce monoclonal antibodies reactive with C3b/C4b CR-like polypeptides.

Monoclonal antibodies of the invention may be modified for use as therapeutics. One embodiment is a "chimeric" antibody in which a portion of the heavy and/or light chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies, so long as they exhibit the desired biological activity. See, U.S. Patent No. 4,816,567; Morrison *et al.*, *Proc. Natl. Acad. Sci.*, 81:6851-6855 (1985).

In another embodiment, a monoclonal antibody of the invention is a "humanized" antibody. Methods for

humanizing non-human antibodies are well known in the art. See U.S. Patent Nos. 5,585,089, and 5,693,762. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. Humanization can be performed, for example, using methods described in the art (Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature*, 332:323-327 (1988); Verhoeyen *et al.*, *Science* 239:1534-1536 (1988)), by substituting at least a portion of a rodent complementarity-determining region (CDR) for the corresponding regions of a human antibody.

Also encompassed by the invention are human antibodies which bind C3b/C4b CR-like polypeptides. Using transgenic animals (*e.g.*, mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production such antibodies are produced by immunization with a C3b/C4b CR-like antigen (*i.e.*, having at least 6 contiguous amino acids), optionally conjugated to a carrier. See, for example, Jakobovits *et al.*, *Proc. Natl. Acad. Sci.*, 90:2551-2555 (1993); Jakobovits *et al.*, *Nature* 362:255-258 (1993); Bruggemann *et al.*, *Year in Immuno.*, 7:33 (1993). In one method, such transgenic animals are produced by incapacitating the endogenous loci encoding the heavy and light immunoglobulin chains therein, and inserting loci encoding human heavy and light chain proteins into the genome thereof. Partially modified animals, that is those having less than the full complement of modifications, are then cross-bred to obtain an animal having all of the desired immune system modifications. When administered an immunogen, these transgenic animals produce antibodies with human

(rather than *e.g.*, murine) amino acid sequences, including variable regions which are immunospecific for these antigens. See PCT application nos. PCT/US96/05928 and PCT/US93/06926. Additional methods are described in U.S. Patent No. 5,545,807, PCT application nos. PCT/US91/245, PCT/GB89/01207, and in EP 546073B1 and EP 546073A1. Human antibodies may also be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

In an alternative embodiment, human antibodies can be produced from phage-display libraries (Hoogenboom *et al.*, *J. Mol. Biol.* 227:381 (1991); Marks *et al.*, *J. Mol. Biol.* 222:581 (1991). These processes mimic immune selection through the display of antibody repertoires on the surface of filamentous bacteriophage, and subsequent selection of phage by their binding to an antigen of choice. One such technique is described in PCT Application no. PCT/US98/17364, which describes the isolation of high affinity and functional agonistic antibodies for MPL- and msk- receptors using such an approach.

Chimeric, CDR grafted, and humanized antibodies are typically produced by recombinant methods. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein. In a preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Monoclonal (*e.g.*, human) antibodies may be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

The anti-C3b/C4b CR-like antibodies of the invention may be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays (Zola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc., 1987)) for the detection and quantitation of C3b/C4b CR-like polypeptides. The antibodies will bind C3b/C4b CR-like polypeptides with an affinity which is appropriate for the assay method being employed.

For diagnostic applications, in certain embodiments, anti-C3b/C4b CR-like antibodies may be labeled with a detectable moiety. The detectable moiety can be any one which is capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I, a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or an enzyme, such as alkaline phosphatase, □-galactosidase, or horseradish peroxidase (Bayer *et al.*, *Meth. Enz.*, 184:138-163 (1990)).

Competitive binding assays rely on the ability of a labeled standard (*e.g.*, a C3b/C4b CR-like polypeptide, or an immunologically reactive portion thereof) to compete with the test sample analyte (an C3b/C4b CR-like polypeptide) for binding with a limited amount of anti C3b/C4b CR-like antibody. The amount of a C3b/C4b CR-like polypeptide in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound,

the antibodies typically are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte which remain unbound.

Sandwich assays typically involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected and/or quantitated. In a sandwich assay, the test sample analyte is typically bound by a first antibody which is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three part complex. See, *e.g.*, U.S. Patent No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assays). For example, one type of sandwich assay is an enzyme-linked immunosorbent assay (ELISA), in which case the detectable moiety is an enzyme.

The selective binding agents, including anti-C3b/C4b CR-like antibodies, also are useful for *in vivo* imaging. An antibody labeled with a detectable moiety may be administered to an animal, preferably into the bloodstream, and the presence and location of the labeled antibody in the host is assayed. The antibody may be labeled with any moiety that is detectable in an animal, whether by nuclear magnetic resonance, radiology, or other detection means known in the art.

Selective binding agents of the invention, including antibodies, may be used as therapeutics. These therapeutic agents are generally agonists or antagonists, in that they either enhance or reduce, respectively, at least one of the biological activities of a C3b/C4b CR-like polypeptide. In one embodiment, antagonist antibodies of the invention are antibodies or binding fragments thereof which are capable of specifically binding to a C3b/C4b CR-like polypeptide and which are capable of inhibiting or eliminating the functional activity of a C3b/C4b CR-like polypeptide *in vivo* or *in vitro*. In preferred embodiments, the selective binding agent, *e.g.*, an antagonist antibody, will inhibit the functional activity of a C3b/C4b CR-like polypeptide by at least about 50%, and preferably by at least about 80%. In another embodiment, the selective binding agent may be an antibody that is capable of interacting with a C3b/C4b CR-like binding partner (a ligand or receptor) thereby inhibiting or eliminating C3b/C4b CR-like activity *in vitro* or *in vivo*. Selective binding agents, including agonist and antagonist anti-C3b/C4b CR-like antibodies, are identified by screening assays which are well known in the art.

The invention also relates to a kit comprising C3b/C4b CR-like selective binding agents (such as antibodies) and other reagents useful for detecting C3b/C4b CR-like polypeptide levels in biological samples. Such reagents may include, a detectable label, blocking serum, positive and negative control samples, and detection reagents.

C3b/C4b CR-like polypeptides can be used to clone

C3b/C4b CR-like ligand(s) using an "expression cloning" strategy. Radiolabeled (125-Iodine) C3b/C4b CR-like polypeptide or "affinity/activity-tagged" C3b/C4b CR-like polypeptide (such as an Fc fusion or an alkaline phosphatase fusion) can be used in binding assays to identify a cell type or cell line or tissue that expresses C3b/C4b CR-like ligand(s). RNA isolated from such cells or tissues can then be converted to cDNA, cloned into a mammalian expression vector, and transfected into mammalian cells (for example, COS, or 293) to create an expression library. Radiolabeled or tagged C3b/C4b CR-like polypeptide can then be used as an affinity reagent to identify and isolate the subset of cells in this library expressing C3b/C4b CR-like ligand(s). DNA is then isolated from these cells and transfected into mammalian cells to create a secondary expression library in which the fraction of cells expressing C3b/C4b CR-like ligand(s) would be many-fold higher than in the original library. This enrichment process can be repeated iteratively until a single recombinant clone containing a C3b/C4b CR-like ligand is isolated. Isolation of C3b/C4b CR-like ligand(s) is useful for identifying or developing novel agonists and antagonists of the C3b/C4b CR-like signaling pathway. Such agonists and antagonists include C3b/C4b CR-like ligand(s), anti-C3b/C4b CR-like ligand antibodies, small molecules or antisense oligonucleotides.

<u>Assaying for other modulators of C3b/C4b CR-like Polypeptide activity</u>

In some situations, it may be desirable to identify molecules that are modulators, *i.e.*, agonists or antagonists, of the activity of C3b/C4b CR-like

polypeptide. Natural or synthetic molecules that modulate C3b/C4b CR-like polypeptide may be identified using one or more screening assays, such as those described herein. Such molecules may be administered either in an *ex vivo* manner, or in an *in vivo* manner by injection, or by oral delivery, implantation device, or the like.

"Test molecule(s)" refers to the molecule(s) that is/are under evaluation for the ability to modulate (*i.e.*, increase or decrease) the activity of a C3b/C4b CR-like polypeptide. Most commonly, a test molecule will interact directly with a C3b/C4b CR-like polypeptide. However, it is also contemplated that a test molecule may also modulate C3b/C4b CR-like polypeptide activity indirectly, such as by affecting C3b/C4b CR-like gene expression, or by binding to a C3b/C4b CR-like binding partner (*e.g.*, receptor or ligand). In one embodiment, a test molecule will bind to a C3b/C4b CR-like polypeptide with an affinity constant of at least about 10^{-6} M, preferably about 10^{-8} M, more preferably about 10^{-9} M, and even more preferably about 10^{-10} M.

Methods for identifying compounds which interact with C3b/C4b CR-like polypeptides are encompassed by the present invention. In certain embodiments, a C3b/C4b CR-like polypeptide is incubated with a test molecule under conditions which permit the interaction of the test molecule with a C3b/C4b CR-like polypeptide, and the extent of the interaction can be measured. The test molecule(s) can be screened in a substantially purified form or in a crude mixture.

In certain embodiments, a C3b/C4b CR-like polypeptide agonist or antagonist may be a protein, peptide, carbohydrate, lipid, or small molecular weight molecule which interacts with C3b/C4b CR-like polypeptide to regulate its activity. Molecules which regulate C3b/C4b CR-like polypeptide expression include nucleic acids which are complementary to nucleic acids encoding a C3b/C4b CR-like polypeptide, or are complementary to nucleic acids sequences which direct or control the expression of C3b/C4b CR-like polypeptide, and which act as anti-sense regulators of expression.

Once a set of test molecules has been identified as interacting with a C3b/C4b CR-like polypeptide, the molecules may be further evaluated for their ability to increase or decrease C3b/C4b CR-like polypeptide activity. The measurement of the interaction of test molecules with C3b/C4b CR-like polypeptides may be carried out in several formats, including cell-based binding assays, membrane binding assays, solution-phase assays and immunoassays. In general, test molecules are incubated with a C3b/C4b CR-like polypeptide for a specified period of time, and C3b/C4b CR-like polypeptide activity is determined by one or more assays for measuring biological activity.

The interaction of test molecules with C3b/C4b CR-like polypeptides may also be assayed directly using polyclonal or monoclonal antibodies in an immunoassay. Alternatively, modified forms of C3b/C4b CR-like polypeptides containing epitope tags as described herein may be used in immunoassays.

In the event that C3b/C4b CR-like polypeptides display biological activity through an interaction with a binding partner (*e.g.*, a receptor or a ligand), a variety of *in vitro* assays may be used to measure the binding of a C3b/C4b CR-like polypeptide to the corresponding binding partner (such as a selective binding agent, receptor, or ligand). These assays may be used to screen test molecules for their ability to increase or decrease the rate and/or the extent of binding of a C3b/C4b CR-like polypeptide to its binding partner. In one assay, a C3b/C4b CR-like polypeptide is immobilized in the wells of a microtiter plate. Radiolabeled C3b/C4b CR-like binding partner (for example, iodinated C3b/C4b CR-like binding partner) and the test molecule(s) can then be added either one at a time (in either order) or simultaneously to the wells. After incubation, the wells can be washed and counted, using a scintillation counter, for radioactivity to determine the extent to which the binding partner bound to C3b/C4b CR-like polypeptide. Typically, the molecules will be tested over a range of concentrations, and a series of control wells lacking one or more elements of the test assays can be used for accuracy in the evaluation of the results. An alternative to this method involves reversing the "positions" of the proteins, *i.e.*, immobilizing C3b/C4b CR-like binding partner to the microtiter plate wells, incubating with the test molecule and radiolabeled C3b/C4b CR-like polypeptide, and determining the extent of C3b/C4b CR-like polypeptide binding. See, for example, chapter 18, *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, New York, NY (1995).

As an alternative to radiolabelling, a C3b/C4b CR-like polypeptide or its binding partner may be conjugated to biotin and the presence of biotinylated protein can then be detected using streptavidin linked to an enzyme, such as horseradish peroxidase (HRP) or alkaline phosphatase (AP), that can be detected colorometrically, or by fluorescent tagging of streptavidin. An antibody directed to a C3b/C4b CR-like polypeptide or to a C3b/C4b CR-like binding partner and conjugated to biotin may also be used and can be detected after incubation with enzyme-linked streptavidin linked to AP or HRP.

An C3b/C4b CR-like polypeptide or a C3b/C4b CR-like binding partner can also be immobilized by attachment to agarose beads, acrylic beads or other types of such inert solid phase substrates. The substrate-protein complex can be placed in a solution containing the complementary protein and the test compound. After incubation, the beads can be precipitated by centrifugation, and the amount of binding between a C3b/C4b CR-like polypeptide and its binding partner can be assessed using the methods described herein. Alternatively, the substrate-protein complex can be immobilized in a column, and the test molecule and complementary protein are passed through the column. The formation of a complex between a C3b/C4b CR-like polypeptide and its binding partner can then be assessed using any of the techniques set forth herein, *i.e.*, radiolabelling, antibody binding, or the like.

Another *in vitro* assay that is useful for identifying a test molecule which increases or

decreases the formation of a complex between a C3b/C4b Complement Receptor polypeptide and a C3b/C4b CR-like binding partner is a surface plasmon resonance detector system such as the BIAcore assay system (Pharmacia, Piscataway, NJ). The BIAcore system may be carried out using the manufacturer's protocol. This assay essentially involves the covalent binding of either C3b/C4b CR-like polypeptide or a C3b/C4b CR-like binding partner to a dextran-coated sensor chip which is located in a detector. The test compound and the other complementary protein can then be injected, either simultaneously or sequentially, into the chamber containing the sensor chip. The amount of complementary protein that binds can be assessed based on the change in molecular mass which is physically associated with the dextran-coated side of the sensor chip; the change in molecular mass can be measured by the detector system.

In some cases, it may be desirable to evaluate two or more test compounds together for their ability to increase or decrease the formation of a complex between a C3b/C4b CR-like polypeptide and a C3b/C4b CR-like binding partner. In these cases, the assays set forth herein can be readily modified by adding such additional test compound(s) either simultaneous with, or subsequent to, the first test compound. The remainder of the steps in the assay are as set forth herein.

In vitro assays such as those described herein may be used advantageously to screen large numbers of compounds for effects on complex formation by C3b/C4b CR-like polypeptide and C3b/C4b CR-like binding

partner. The assays may be automated to screen compounds generated in phage display, synthetic peptide, and chemical synthesis libraries.

Compounds which increase or decrease the formation of a complex between a C3b/C4b CR-like polypeptide and a C3b/C4b CR-like binding partner may also be screened in cell culture using cells and cell lines expressing either C3b/C4b CR-like polypeptide or C3b/C4b CR-like binding partner. Cells and cell lines may be obtained from any mammal, but preferably will be from human or other primate, canine, or rodent sources. The binding of a C3b/C4b CR-like polypeptide to cells expressing C3b/C4b CR-like binding partner at the surface is evaluated in the presence or absence of test molecules, and the extent of binding may be determined by, for example, flow cytometry using a biotinylated antibody to a C3b/C4b CR-like binding partner. Cell culture assays can be used advantageously to further evaluate compounds that score positive in protein binding assays described herein.

Cell cultures can also be used to screen the impact of a drug candidate. For example, drug candidates may decrease or increase the expression of the C3b/C4b CR-like gene. In certain embodiments, the amount of C3b/C4b CR-like polypeptide that is produced may be measured after exposure of the cell culture to the drug candidate. In certain embodiments, one may detect the actual impact of the drug candidate on the cell culture. For example, the overexpression of a particular gene may have a particular impact on the cell culture. In such cases, one may test a drug candidate's ability to increase or decrease the

expression of the gene or its ability to prevent or inhibit a particular impact on the cell culture. In other examples, the production of a particular metabolic product such as a fragment of a polypeptide, may result in, or be associated with, a disease or pathological condition. In such cases, one may test a drug candidate's ability to decrease the production of such a metabolic product in a cell culture.

A yeast two hybrid system (Chien *et al.*, *Proc. Natl. Acad. Sci. USA*, 88:9578-9583 (1991)) can be used to identify novel polypeptides that bind to, or interact with, C3b/C4b CR-like polypeptides. As an example, hybrid constructs comprising DNA encoding a cytoplasmic domain of a C3b/C4b CR-like polypeptide fused to a yeast GAL4-DNA binding domain may be used as a two-hybrid bait plasmid. Positive clones emerging from the screening may be characterized further to identify interacting proteins.

Internalizing Proteins

The *tat* protein sequence (from HIV) can be used to internalize proteins into a cell. See *e.g.*, Falwell *et al.*, *Proc. Natl. Acad. Sci.*, 91:664-668 (1994). For example, an 11 amino acid sequence (YGRKKRRQRRR) of the HIV tat protein (termed the "protein transduction domain", or TAT PDT) has been described as mediating delivery across the cytoplasmic membrane and the nuclear membrane of a cell. *See* Schwarze *et al.*, *Science*, 285:1569-1572 (1999); and Nagahara *et al.*, *Nature Medicine*, 4:1449-1452 (1998). In these procedures, FITC-constructs (FITC-GGGGYGRKKRRQRRR) are prepared which bind to cells as observed by

fluorescence-activated cell sorting (FACS) analysis, and these constructs penetrate tissues after i.p. administration. Next, tat-bgal fusion proteins are constructed. Cells treated with this construct demonstrated b-gal activity. Following injection, a number of tissues, including liver, kidney, lung, heart, and brain tissue have been found to demonstrate expression using these procedures. It is believed that these constructions underwent some degree of unfolding in order to enter the cell; as such, refolding may be required after entering the cell.

It will thus be appreciated that the tat protein sequence may be used to internalize a desired protein or polypeptide into a cell. For example, using the *tat* protein sequence, a C3b/C4b CR-like antagonist (such as an anti-C3b/C4b CR-like selective binding agent, small molecule, soluble receptor, or antisense oligonucleotide) can be administered intracellularly to inhibit the activity of a C3b/C4b CR-like molecule. As used herein, the term "C3b/C4b CR-like molecule" refers to both C3b/C4b CR-like nucleic acid molecules and C3b/C4b CR-like polypeptides as defined herein. Where desired, the C3b/C4b CR-like protein itself may also be internally administered to a cell using these procedures. *See also*, Strauss, E., "Introducing Proteins Into the Body's Cells", *Science*, 285:1466-1467 (1999).

Therapeutic Uses

A non-exclusive list of acute and chronic diseases which can be treated, diagnosed, ameliorated, or prevented with the polypeptides and nucleic acids of the invention is set forth below.

C3b/C4b CR-related polypeptides may act to stimulate the activation of the complement system, which acts alone and in conjunction with antibodies to destroy cells that are foreign to the host and is a main defense against bacterial and viral infections. The ability of a binding partner to bind to and activate C3b/C4b CR-related polypeptide or protein may lead to complement activation. Such a binding partner can be an agonist of C3b/C4b-CR related polypeptide or protein, such as antibody, peptibody, peptide, carbohydrate, polynucleotide, or small molecular weight organic molecule. Agonists of C3b/C4b CR-related polypeptides or proteins may be used to prevent and treat conditions characterized by insufficient or defective complement activation, such as bacterial and viral infections.

Alternatively, it may be desirable to use an antagonist of C3b/C4b CR-related polypeptide or protein to block complement activation. An antagonist would be useful for preventing and treating conditions characterized by excessive complement activation, particularly immune system disorders such as rheumatoid arthritis, psioriatic arthritis, inflammatory arthritis, osteoarthritis, inflammatory joint disease, autoimmune disease, multiple sclerosis, lupus, diabetes, inflammatory bowel disease, transplant rejection, and graft versus host disease. Antagonists would also be useful for prevent or treating undesired complement-mediated damage to cells and tissues. In one embodiment, an antagonist comprises a soluble domain of a C3b/C4b CR-related polypeptide or protein.

Other uses for agonists and antagonists of C3b/C4b CR-like molecules include the diagnosis, prevention and

treatment of nervous system disorders, such as stroke, Alzheimer's disease, brain injury, and Parkinson's disease; damaged tissues, such as by wounds and burns; ischemic conditions, such as atherosclerosis, restenosis, myocardial infarction, angioplasty, hypertension, and ischemia; metabolic disorders, such as obesity, diabetes, and cachexia; and reproductive disorders, infertility, miscarriage, preterm labor and delivery, and endometriosis.

C3b/C4b CR-like Compositions and Administration

Therapeutic compositions are within the scope of the present invention. Such C3B/C4B CR-like pharmaceutical compositions may comprise a therapeutically effective amount of a C3b/C4b CR-like polypeptide or a C3b/C4b CR-like nucleic acid molecule in admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration. Pharmaceutical compositions may comprise a therapeutically effective amount of one or more C3b/C4b CR-like selective binding agents in admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration.

Acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

The pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility,

stability, rate of dissolution or release, adsorption or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine), antimicrobials, antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite), buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, other organic acids), bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)), complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin), fillers, monosaccharides, disaccharides, and other carbohydrates (such as glucose, mannose, or dextrins), proteins (such as serum albumin, gelatin or immunoglobulins), coloring, flavoring and diluting agents, emulsifying agents, hydrophilic polymers (such as polyvinylpyrrolidone), low molecular weight polypeptides, salt-forming counterions (such as sodium), preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide), solvents (such as glycerin, propylene glycol or polyethylene glycol), sugar alcohols (such as mannitol or sorbitol), suspending agents, surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal), stability enhancing agents (sucrose or sorbitol), tonicity enhancing agents (such as alkali metal halides (preferably sodium or potassium chloride), mannitol

sorbitol), delivery vehicles, diluents, excipients and/or pharmaceutical adjuvants. (*Remington's Pharmaceutical Sciences*, 18th Edition, A.R. Gennaro, ed., Mack Publishing Company [1990]).

The optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format, and desired dosage. See for example, *Remington's Pharmaceutical Sciences*, *supra*. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the C3b/C4b CR-like molecule.

The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution, or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Other exemplary pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute therefor. In one embodiment of the present invention, C3b/C4b CR-like polypeptide compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (*Remington's Pharmaceutical Sciences*, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, the C3b/C4b CR-like polypeptide product may be formulated as a lyophilizate

using appropriate excipients such as sucrose.

The C3b/C4b CR-like pharmaceutical compositions can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the skill of the art.

The formulation components are present in concentrations that are acceptable to the site of administration. For example, buffers are used to maintain the composition at physiological pH or at slightly lower pH, typically within a pH range of from about 5 to about 8.

When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired C3b/C4b CR-like molecule in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which a C3b/C4b CR-like molecule is formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (polylactic acid, polyglycolic acid), or beads, or liposomes, that provides for the controlled or sustained release of the product which may then be delivered as a depot injection. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Other suitable

means for the introduction of the desired molecule include implantable drug delivery devices.

In one embodiment, a pharmaceutical composition may be formulated for inhalation. For example, a C3b/C4b CR-like molecule may be formulated as a dry powder for inhalation. C3b/C4b CR-like polypeptide or C3b/C4b CR-like nucleic acid molecule inhalation solutions may also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions may be nebulized. Pulmonary administration is further described in PCT application no. PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins.

It is also contemplated that certain formulations may be administered orally. In one embodiment of the present invention, C3b/C4b CR-like molecules which are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the C3b/C4b CR-like molecule. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

Another pharmaceutical composition may involve an effective quantity of C3b/C4b CR-like molecules in a mixture with non-toxic excipients which are suitable

for the manufacture of tablets. By dissolving the tablets in sterile water, or other appropriate vehicle, solutions can be prepared in unit dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

Additional C3b/C4b CR-like pharmaceutical compositions will be evident to those skilled in the art, including formulations involving C3b/C4b CR-like polypeptides in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT/US93/00829 which describes controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, *e.g.* films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (U.S. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, *Biopolymers*, 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer *et al.*, *J. Biomed. Mater. Res.*, 15:167-277 (1981) and Langer, *Chem. Tech.*, 12:98-105 (1982)), ethylene vinyl acetate (Langer *et al.*, *supra*) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also may include

liposomes, which can be prepared by any of several methods known in the art. See *e.g.*, Eppstein *et al.*, *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); EP 36,676; EP 88,046; EP 143,949.

The C3b/C4b CR-like pharmaceutical composition to be used for *in vivo* administration typically must be sterile. This may be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using these methods may be conducted either prior to, or following, lyophilization and reconstitution. The composition for parenteral administration may be stored in lyophilized form or in solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) requiring reconstitution prior to administration.

In a specific embodiment, the present invention is directed to kits for producing a single-dose administration unit. The kits may each contain both a first container having a dried protein and a second container having an aqueous formulation. Also included within the scope of this invention are kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes).

An effective amount of a C3b/C4b CR-like pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the C3b/C4b CR-like molecule is being used, the route of administration, and the size (body weight, body surface or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 μg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In other embodiments, the dosage may range from 0.1 μg/kg up to about 100 mg/kg; or 1 μg/kg up to about 100 mg/kg; or 5 μg/kg up to about 100 mg/kg.

The frequency of dosing will depend upon the pharmacokinetic parameters of the C3b/C4b CR-like molecule in the formulation used. Typically, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages

may be ascertained through use of appropriate dose-response data.

The route of administration of the pharmaceutical composition is in accord with known methods, *e.g.* oral, injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, or intralesional routes, or by sustained release systems or implantation device. Where desired, the compositions may be administered by bolus injection or continuously by infusion, or by implantation device.

Alternatively or additionally, the composition may be administered locally via implantation of a membrane, sponge, or other appropriate material on to which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed release bolus, or continuous administration.

In some cases, it may be desirable to use C3b/C4b CR-like pharmaceutical compositions in an *ex vivo* manner. In such instances, cells, tissues, or organs that have been removed from the patient are exposed to C3b/C4b CR-like pharmaceutical compositions after which the cells, tissues and/or organs are subsequently implanted back into the patient.

In other cases, a C3b/C4b CR-like polypeptide can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the

polypeptide. Such cells may be animal or human cells, and may be autologous, heterologous, or xenogeneic. Optionally, the cells may be immortalized. In order to decrease the chance of an immunological response, the cells may be encapsulated to avoid infiltration of surrounding tissues. The encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

Additional embodiments of the present invention relate to cells and methods (*e.g.*, homologous recombination and/or other recombinant production methods) for both the *in vitro* production of therapeutic polypeptides and for the production and delivery of therapeutic polypeptides by gene therapy or cell therapy. Homologous and other recombination methods may be used to modify a cell that contains a normally transcriptionally silent C3b/C4b CR-like gene, or an under expressed gene, and thereby produce a cell which expresses therapeutically efficacious amounts of C3b/C4b CR-like polypeptides.

Homologous recombination is a technique originally developed for targeting genes to induce or correct mutations in transcriptionally active genes (Kucherlapati, *Prog. in Nucl. Acid Res. & Mol. Biol.*, 36:301, 1989). The basic technique was developed as a method for introducing specific mutations into specific regions of the mammalian genome (Thomas *et al.*, *Cell*, 44:419-428, 1986; Thomas and Capecchi, *Cell*, 51:503-512, 1987; Doetschman *et al.*, *Proc. Natl. Acad. Sci.*,

85:8583-8587, 1988) or to correct specific mutations within defective genes (Doetschman *et al.*, *Nature*, 330:576-578, 1987). Exemplary homologous recombination techniques are described in U.S. Patent No. 5,272,071 (EP 9193051, EP Publication No. 505500; PCT/US90/07642, International Publication No. WO 91/09955).

Through homologous recombination, the DNA sequence to be inserted into the genome can be directed to a specific region of the gene of interest by attaching it to targeting DNA. The targeting DNA is a nucleotide sequence that is complementary (homologous) to a region of the genomic DNA. Small pieces of targeting DNA that are complementary to a specific region of the genome are put in contact with the parental strand during the DNA replication process. It is a general property of DNA that has been inserted into a cell to hybridize, and therefore, recombine with other pieces of endogenous DNA through shared homologous regions. If this complementary strand is attached to an oligonucleotide that contains a mutation or a different sequence or an additional nucleotide, it too is incorporated into the newly synthesized strand as a result of the recombination. As a result of the proofreading function, it is possible for the new sequence of DNA to serve as the template. Thus, the transferred DNA is incorporated into the genome.

Attached to these pieces of targeting DNA are regions of DNA which may interact with or control the expression of a C3b/C4b CR-like polypeptide, *e.g.*, flanking sequences. For example, a promoter/enhancer element, a suppresser, or an exogenous transcription modulatory element is inserted in the genome of the

intended host cell in proximity and orientation sufficient to influence the transcription of DNA encoding the desired C3b/C4b CR-like polypeptide. The control element controls a portion of the DNA present in the host cell genome. Thus, the expression of the desired C3b/C4b CR-like polypeptide may be achieved not by transfection of DNA that encodes the C3b/C4b CR-like gene itself, but rather by the use of targeting DNA (containing regions of homology with the endogenous gene of interest) coupled with DNA regulatory segments that provide the endogenous gene sequence with recognizable signals for transcription of a C3b/C4b CR-like polypeptide.

In an exemplary method, the expression of a desired targeted gene in a cell (*i.e.*, a desired endogenous cellular gene) is altered via homologous recombination into the cellular genome at a preselected site, by the introduction of DNA which includes at least a regulatory sequence, an exon and a splice donor site. These components are introduced into the chromosomal (genomic) DNA in such a manner that this, in effect, results in the production of a new transcription unit (in which the regulatory sequence, the exon and the splice donor site present in the DNA construct are operatively linked to the endogenous gene). As a result of the introduction of these components into the chromosomal DNA, the expression of the desired endogenous gene is altered.

Altered gene expression, as described herein, encompasses activating (or causing to be expressed) a gene which is normally silent (unexpressed) in the cell as obtained, as well as increasing the expression of a

gene which is not expressed at physiologically significant levels in the cell as obtained. The embodiments further encompass changing the pattern of regulation or induction such that it is different from the pattern of regulation or induction that occurs in the cell as obtained, and reducing (including eliminating) the expression of a gene which is expressed in the cell as obtained.

One method by which homologous recombination can be used to increase, or cause, C3b/C4b CR-like polypeptide production from a cell's endogenous C3b/C4b CR-like gene involves first using homologous recombination to place a recombination sequence from a site-specific recombination system (*e.g.*, Cre/loxP, FLP/FRT) (Sauer, *Current Opinion In Biotechnology*, 5:521-527, 1994; Sauer, *Methods In Enzymology*, 225:890-900, 1993) upstream (that is, 5' to) of the cell's endogenous genomic C3b/C4b CR-like polypeptide coding region. A plasmid containing a recombination site homologous to the site that was placed just upstream of the genomic C3b/C4b CR-like polypeptide coding region is introduced into the modified cell line along with the appropriate recombinase enzyme. This recombinase causes the plasmid to integrate, via the plasmid's recombination site, into the recombination site located just upstream of the genomic C3b/C4b CR-like polypeptide coding region in the cell line (Baubonis and Sauer, *Nucleic Acids Res.*, 21:2025-2029, 1993; O'Gorman *et al.*, *Science*, 251:1351-1355, 1991). Any flanking sequences known to increase transcription (*e.g.*, enhancer/promoter, intron, translational enhancer), if properly positioned in this plasmid,

would integrate in such a manner as to create a new or modified transcriptional unit resulting in *de novo* or increased C3b/C4b CR-like polypeptide production from the cell's endogenous C3b/C4b CR-like gene.

A further method to use the cell line in which the site specific recombination sequence had been placed just upstream of the cell's endogenous genomic C3b/C4b CR-like polypeptide coding region is to use homologous recombination to introduce a second recombination site elsewhere in the cell line's genome. The appropriate recombinase enzyme is then introduced into the two-recombination-site cell line, causing a recombination event (deletion, inversion, translocation) (Sauer, *Current Opinion In Biotechnology*, *supra*, 1994; Sauer, *Methods In Enzymology*, *supra*, 1993) that would create a new or modified transcriptional unit resulting in *de novo* or increased C3b/C4b CR-like polypeptide production from the cell's endogenous C3b/C4b CR-like gene.

An additional approach for increasing, or causing, the expression of C3b/C4b CR-like polypeptide from a cell's endogenous C3b/C4b CR-like gene involves increasing, or causing, the expression of a gene or genes (*e.g.*, transcription factors) and/or decreasing the expression of a gene or genes (*e.g.*, transcriptional repressors) in a manner which results in *de novo* or increased C3b/C4b CR-like polypeptide production from the cell's endogenous C3b/C4b CR-like gene. This method includes the introduction of a non-naturally occurring polypeptide (*e.g.*, a polypeptide comprising a site specific DNA binding domain fused to a transcriptional factor domain) into the cell such

that *de novo* or increased C3b/C4b CR-like polypeptide production from the cell's endogenous C3b/C4b CR-like gene results.

The present invention further relates to DNA constructs useful in the method of altering expression of a target gene. In certain embodiments, the exemplary DNA constructs comprise: (a) one or more targeting sequences; (b) a regulatory sequence; (c) an exon; and (d) an unpaired splice-donor site. The targeting sequence in the DNA construct directs the integration of elements (a)-(d) into a target gene in a cell such that the elements (b)-(d) are operatively linked to sequences of the endogenous target gene. In another embodiment, the DNA constructs comprise: (a) one or more targeting sequences, (b) a regulatory sequence, (c) an exon, (d) a splice-donor site, (e) an intron, and (f) a splice-acceptor site, wherein the targeting sequence directs the integration of elements (a)-(f) such that the elements of (b)-(f) are operatively linked to the endogenous gene. The targeting sequence is homologous to the preselected site in the cellular chromosomal DNA with which homologous recombination is to occur. In the construct, the exon is generally 3' of the regulatory sequence and the splice-donor site is 3' of the exon.

If the sequence of a particular gene is known, such as the nucleic acid sequence of C3b/C4b CR-like polypeptide presented herein, a piece of DNA that is complementary to a selected region of the gene can be synthesized or otherwise obtained, such as by appropriate restriction of the native DNA at specific recognition sites bounding the region of interest.

This piece serves as a targeting sequence(s) upon insertion into the cell and will hybridize to its homologous region within the genome. If this hybridization occurs during DNA replication, this piece of DNA, and any additional sequence attached thereto, will act as an Okazaki fragment and will be incorporated into the newly synthesized daughter strand of DNA. The present invention, therefore, includes nucleotides encoding a C3b/C4b CR-like polypeptide, which nucleotides may be used as targeting sequences.

C3b/C4b CR-like polypeptide cell therapy, *e.g.*, the implantation of cells producing C3b/C4b CR-like polypeptides, is also contemplated. This embodiment involves implanting cells capable of synthesizing and secreting a biologically active form of C3b/C4b CR-like polypeptide. Such C3b/C4b CR-like polypeptide-producing cells can be cells that are natural producers of C3b/C4b CR-like polypeptides or may be recombinant cells whose ability to produce C3b/C4b CR-like polypeptides has been augmented by transformation with a gene encoding the desired C3b/C4b CR-like polypeptide or with a gene augmenting the expression of C3b/C4b CR-like polypeptide. Such a modification may be accomplished by means of a vector suitable for delivering the gene as well as promoting its expression and secretion. In order to minimize a potential immunological reaction in patients being administered a C3b/C4b CR-like polypeptide, as may occur with the administration of a polypeptide of a foreign species, it is preferred that the natural cells producing C3b/C4b CR-like polypeptide be of human origin and produce human C3b/C4b CR-like polypeptide. Likewise, it is preferred that the recombinant cells producing

C3b/C4b CR-like polypeptide be transformed with an expression vector containing a gene encoding a human C3b/C4b CR-like polypeptide.

Implanted cells may be encapsulated to avoid the infiltration of surrounding tissue. Human or non-human animal cells may be implanted in patients in biocompatible, semipermeable polymeric enclosures or membranes that allow the release of C3b/C4b CR-like polypeptide, but that prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissue. Alternatively, the patient's own cells, transformed to produce C3b/C4b CR-like polypeptides *ex vivo*, may be implanted directly into the patient without such encapsulation.

Techniques for the encapsulation of living cells are known in the art, and the preparation of the encapsulated cells and their implantation in patients may be routinely accomplished. For example, Baetge *et al.* (WO95/05452; PCT/US94/09299) describe membrane capsules containing genetically engineered cells for the effective delivery of biologically active molecules. The capsules are biocompatible and are easily retrievable. The capsules encapsulate cells transfected with recombinant DNA molecules comprising DNA sequences coding for biologically active molecules operatively linked to promoters that are not subject to down regulation *in vivo* upon implantation into a mammalian host. The devices provide for the delivery of the molecules from living cells to specific sites within a recipient. In addition, see U.S. Patent Nos. 4,892,538, 5,011,472, and 5,106,627. A system for

encapsulating living cells is described in PCT Application no. PCT/US91/00157 of Aebischer *et al.* See also, PCT Application no. PCT/US91/00155 of Aebischer *et al.*, Winn *et al.*, *Exper. Neurol.*, 113:322-329 (1991), Aebischer *et al.*, *Exper. Neurol.*, 111:269-275 (1991); and Tresco *et al.*, ASAIO, 38:17-23 (1992).

In vivo and *in vitro* gene therapy delivery of C3b/C4b CR-like polypeptides is also envisioned. One example of a gene therapy technique is to use the C3b/C4b CR-like gene (either genomic DNA, cDNA, and/or synthetic DNA) encoding a C3b/C4b CR-like polypeptide which may be operably linked to a constitutive or inducible promoter to form a "gene therapy DNA construct". The promoter may be homologous or heterologous to the endogenous C3b/C4b CR-like gene, provided that it is active in the cell or tissue type into which the construct will be inserted. Other components of the gene therapy DNA construct may optionally include, DNA molecules designed for site-specific integration (*e.g.*, endogenous sequences useful for homologous recombination), tissue-specific promoter, enhancer(s) or silencer(s), DNA molecules capable of providing a selective advantage over the parent cell, DNA molecules useful as labels to identify transformed cells, negative selection systems, cell specific binding agents (as, for example, for cell targeting), cell-specific internalization factors, and transcription factors to enhance expression by a vector as well as factors to enable vector manufacture.

A gene therapy DNA construct can then be introduced into cells (either *ex vivo* or *in vivo*) using viral or non-viral vectors. One means for introducing

the gene therapy DNA construct is by means of viral vectors as described herein. Certain vectors, such as retroviral vectors, will deliver the DNA construct to the chromosomal DNA of the cells, and the gene can integrate into the chromosomal DNA. Other vectors will function as episomes, and the gene therapy DNA construct will remain in the cytoplasm.

In yet other embodiments, regulatory elements can be included for the controlled expression of the C3b/C4b CR-like gene in the target cell. Such elements are turned on in response to an appropriate effector. In this way, a therapeutic polypeptide can be expressed when desired. One conventional control means involves the use of small molecule dimerizers or rapalogs (as described in WO9641865 (PCT/US96/099486); WO9731898 (PCT/US97/03137) and WO9731899 (PCT/US95/03157) used to dimerize chimeric proteins which contain a small molecule-binding domain and a domain capable of initiating biological process, such as a DNA-binding protein or transcriptional activation protein. The dimerization of the proteins can be used to initiate transcription of the transgene.

An alternative regulation technology uses a method of storing proteins expressed from the gene of interest inside the cell as an aggregate or cluster. The gene of interest is expressed as a fusion protein that includes a conditional aggregation domain which results in the retention of the aggregated protein in the endoplasmic reticulum. The stored proteins are stable and inactive inside the cell. The proteins can be released, however, by administering a drug (*e.g.*, small molecule ligand) that removes the conditional

aggregation domain and thereby specifically breaks apart the aggregates or clusters so that the proteins may be secreted from the cell. See, *Science* 287:816-817, and 826-830 (2000).

Other suitable control means or gene switches include, but are not limited to, the following systems. Mifepristone (RU486) is used as a progesterone antagonist. The binding of a modified progesterone receptor ligand-binding domain to the progesterone antagonist activates transcription by forming a dimer of two transcription factors which then pass into the nucleus to bind DNA. The ligand binding domain is modified to eliminate the ability of the receptor to bind to the natural ligand. The modified steroid hormone receptor system is further described in U.S. 5,364,791; WO9640911, and WO9710337.

Yet another control system uses ecdysone (a fruit fly steroid hormone) which binds to and activates an ecdysone receptor (cytoplasmic receptor). The receptor then translocates to the nucleus to bind a specific DNA response element (promoter from ecdysone-responsive gene). The ecdysone receptor includes a transactivation domain/DNA-binding domain/ligand-binding domain to initiate transcription. The ecdysone system is further described in U.S. 5,514,578; WO9738117; WO9637609; and WO9303162.

Another control means uses a positive tetracycline-controllable transactivator. This system involves a mutated tet repressor protein DNA-binding domain (mutated tet R-4 amino acid changes which resulted in a reverse tetracycline-regulated

transactivator protein, *i.e.*, it binds to a tet operator in the presence of tetracycline) linked to a polypeptide which activates transcription. Such systems are described in U.S. Patent Nos. 5,464,758; 5,650,298 and 5,654,168.

Additional expression control systems and nucleic acid constructs are described in U.S. Patent Nos. 5,741,679 and 5,834,186, to Innovir Laboratories Inc.

In vivo gene therapy may be accomplished by introducing the gene encoding a C3b/C4b CR-like polypeptide into cells via local injection of a C3b/C4b CR-like nucleic acid molecule or by other appropriate viral or non-viral delivery vectors. Hefti, *Neurobiology*, 25:1418-1435 (1994). For example, a nucleic acid molecule encoding a C3b/C4b CR-like polypeptide may be contained in an adeno-associated virus (AAV) vector for delivery to the targeted cells (*e.g.*, Johnson, International Publication No. WO95/34670; International Application No. PCT/US95/07178). The recombinant AAV genome typically contains AAV inverted terminal repeats flanking a DNA sequence encoding a C3b/C4b CR-like polypeptide operably linked to functional promoter and polyadenylation sequences.

Alternative suitable viral vectors include, but are not limited to, retrovirus, adenovirus, herpes simplex virus, lentivirus, hepatitis virus, parvovirus, papovavirus, poxvirus, alphavirus, coronavirus, rhabdovirus, paramyxovirus, and papilloma virus vectors. U.S. Patent No. 5,672,344 describes an *in vivo* viral-mediated gene transfer system involving a

recombinant neurotrophic HSV-1 vector. U.S. Patent No. 5,399,346 provides examples of a process for providing a patient with a therapeutic protein by the delivery of human cells which have been treated *in vitro* to insert a DNA segment encoding a therapeutic protein. Additional methods and materials for the practice of gene therapy techniques are described in U.S. Patent No. 5,631,236 involving adenoviral vectors; U.S. Patent No. 5,672,510 involving retroviral vectors; and U.S. 5,635,399 involving retroviral vectors expressing cytokines.

Nonviral delivery methods include, but are not limited to, liposome-mediated transfer, naked DNA delivery (direct injection), receptor-mediated transfer (ligand-DNA complex), electroporation, calcium phosphate precipitation, and microparticle bombardment (*e.g.*, gene gun). Gene therapy materials and methods may also include the use of inducible promoters, tissue-specific enhancer-promoters, DNA sequences designed for site-specific integration, DNA sequences capable of providing a selective advantage over the parent cell, labels to identify transformed cells, negative selection systems and expression control systems (safety measures), cell-specific binding agents (for cell targeting), cell-specific internalization factors, and transcription factors to enhance expression by a vector as well as methods of vector manufacture. Such additional methods and materials for the practice of gene therapy techniques are described in U.S. Patent No. 4,970,154 involving electroporation techniques; WO96/40958 involving nuclear ligands; U.S. Patent No. 5,679,559 describing a lipoprotein-

containing system for gene delivery; U.S. Patent No. 5,676,954 involving liposome carriers; U.S. Patent No. 5,593,875 concerning methods for calcium phosphate transfection; and U.S. Patent No. 4,945,050 wherein biologically active particles are propelled at cells at a speed whereby the particles penetrate the surface of the cells and become incorporated into the interior of the cells.

It is also contemplated that C3b/C4b CR-like gene therapy or cell therapy can further include the delivery of one or more additional polypeptide(s) in the same or a different cell(s). Such cells may be separately introduced into the patient, or the cells may be contained in a single implantable device, such as the encapsulating membrane described above, or the cells may be separately modified by means of viral vectors.

A means to increase endogenous C3b/C4b CR-like polypeptide expression in a cell via gene therapy is to insert one or more enhancer elements into the C3b/C4b CR-like polypeptide promoter, where the enhancer element(s) can serve to increase transcriptional activity of the C3b/C4b CR-like gene. The enhancer element(s) used will be selected based on the tissue in which one desires to activate the gene(s); enhancer elements known to confer promoter activation in that tissue will be selected. For example, if a gene encoding a C3b/C4b CR-like polypeptide is to be "turned on" in T-cells, the *lck* promoter enhancer element may be used. Here, the functional portion of the transcriptional element to be added may be inserted into a fragment of DNA containing the C3b/C4b CR-like

polypeptide promoter (and optionally, inserted into a vector and/or 5′ and/or 3′ flanking sequence(s), etc.) using standard cloning techniques. This construct, known as a "homologous recombination construct", can then be introduced into the desired cells either *ex vivo* or *in vivo*.

Gene therapy also can be used to decrease C3b/C4b CR-like polypeptide expression by modifying the nucleotide sequence of the endogenous promoter(s). Such modification is typically accomplished via homologous recombination methods. For example, a DNA molecule containing all or a portion of the promoter of the C3b/C4b CR-like gene(s) selected for inactivation can be engineered to remove and/or replace pieces of the promoter that regulate transcription. For example the TATA box and/or the binding site of a transcriptional activator of the promoter may be deleted using standard molecular biology techniques; such deletion can inhibit promoter activity thereby repressing the transcription of the corresponding C3b/C4b CR-like gene. The deletion of the TATA box or the transcription activator binding site in the promoter may be accomplished by generating a DNA construct comprising all or the relevant portion of the C3b/C4b CR-like polypeptide promoter(s) (from the same or a related species as the C3b/C4b CR-like gene(s) to be regulated) in which one or more of the TATA box and/or transcriptional activator binding site nucleotides are mutated via substitution, deletion and/or insertion of one or more nucleotides. As a result, the TATA box and/or activator binding site has decreased activity or is rendered completely inactive. The construct will typically contain at least about 500

bases of DNA that correspond to the native (endogenous) 5′ and 3′ DNA sequences adjacent to the promoter segment that has been modified. The construct may be introduced into the appropriate cells (either *ex vivo* or *in vivo*) either directly or via a viral vector as described herein. Typically, the integration of the construct into the genomic DNA of the cells will be via homologous recombination, where the 5′ and 3′ DNA sequences in the promoter construct can serve to help integrate the modified promoter region via hybridization to the endogenous chromosomal DNA.

Additional Uses of C3b/C4b CR-like Nucleic Acids and Polypeptides

Nucleic acid molecules of the present invention (including those that do not themselves encode biologically active polypeptides) may be used to map the locations of the C3b/C4b CR-like gene and related genes on chromosomes. Mapping may be done by techniques known in the art, such as PCR amplification and *in situ* hybridization.

C3b/C4b CR-like nucleic acid molecules (including those that do not themselves encode biologically active polypeptides), may be useful as hybridization probes in diagnostic assays to test, either qualitatively or quantitatively, for the presence of a C3b/C4b CR-like DNA or corresponding RNA in mammalian tissue or bodily fluid samples.

The C3b/C4b CR-like polypeptides may be used (simultaneously or sequentially) in combination with one or more cytokines, growth factors, antibiotics, anti-inflammatories, and/or chemotherapeutic agents as

is appropriate for the indication being treated.

Other methods may also be employed where it is desirable to inhibit the activity of one or more C3b/C4b CR-like polypeptides. Such inhibition may be effected by nucleic acid molecules which are complementary to and hybridize to expression control sequences (triple helix formation) or to C3b/C4b CR-like mRNA. For example, antisense DNA or RNA molecules, which have a sequence that is complementary to at least a portion of the selected C3b/C4b CR-like gene(s) can be introduced into the cell. Anti-sense probes may be designed by available techniques using the sequence of C3b/C4b CR-like polypeptide disclosed herein. Typically, each such antisense molecule will be complementary to the start site (5' end) of each selected C3b/C4b CR-like gene. When the antisense molecule then hybridizes to the corresponding C3b/C4b CR-like mRNA, translation of this mRNA is prevented or reduced. Anti-sense inhibitors provide information relating to the decrease or absence of a C3b/C4b CR-like polypeptide in a cell or organism.

Alternatively, gene therapy may be employed to create a dominant-negative inhibitor of one or more C3b/C4b CR-like polypeptides. In this situation, the DNA encoding a mutant polypeptide of each selected C3b/C4b CR-like polypeptide can be prepared and introduced into the cells of a patient using either viral or non-viral methods as described herein. Each such mutant is typically designed to compete with endogenous polypeptide in its biological role.

In addition, a C3b/C4b CR-like polypeptide, whether biologically active or not, may be used as an

immunogen, that is, the polypeptide contains at least one epitope to which antibodies may be raised. Selective binding agents that bind to a C3b/C4b CR-like polypeptide (as described herein) may be used for *in vivo* and *in vitro* diagnostic purposes, including, but not limited to, use in labeled form to detect the presence of C3b/C4b CR-like polypeptide in a body fluid or cell sample. The antibodies may also be used to prevent, treat, or diagnose a number of diseases and disorders, including those recited herein. The antibodies may bind to a C3b/C4b CR-like polypeptide so as to diminish or block at least one activity characteristic of a C3b/C4b CR-like polypeptide, or may bind to a polypeptide to increase at least one activity characteristic of a C3b/C4b CR-like polypeptide (including by increasing the pharmacokinetics of the C3b/C4b CR-like polypeptide).

WHAT IS CLAIMED

1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6;

(b) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of (a) or (b), wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(d) a nucleotide sequence complementary to any of (a)-(c).

2. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(b) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, wherein the encoded polypeptide has an activity of the

polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6; (a); or (b) encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6, or (a)-(c) comprising a fragment of at least about 16 nucleotides;

(e) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a)-(d), wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(f) a nucleotide sequence complementary to any of (a)-(c).

3. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(b) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid insertion, wherein

the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid deletion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 which has a C- and/or N- terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(e) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(f) a nucleotide sequence of (a)-(e) comprising a fragment of at least about 16 nucleotides;

(g) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a)-(f), wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(h) a nucleotide sequence complementary to any of (a)-(e).

4. A vector comprising the nucleic acid molecule of Claims 1, 2, or 3.

5. A host cell comprising the vector of Claim 4.

6. The host cell of Claim 5 that is a eukaryotic cell.

7. The host cell of Claim 5 that is a prokaryotic cell.

8. A process of producing a C3b/C4b CR-like polypeptide comprising culturing the host cell of Claim 5 under suitable conditions to express the polypeptide, and optionally isolating the polypeptide from the culture.

9. A polypeptide produced by the process of Claim 8.

10. The process of Claim 8, wherein the nucleic acid molecule comprises promoter DNA other than the promoter DNA for the native C3b/C4b CR-like polypeptide operatively linked to the DNA encoding the C3b/C4b CR-like polypeptide.

11. The isolated nucleic acid molecule according to Claim 2 wherein the percent identity is determined using a computer program selected from the group consisting of GAP, BLASTP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.

12. A process for determining whether a compound inhibits C3b/C4b CR-like polypeptide activity or production comprising exposing a cell according to Claims 5, 6, or 7 to the compound, and measuring C3b/C4b CR-like polypeptide activity or production in said cell.

13. An isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

14. An isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) an amino acid sequence of the mature C3b/C4b CR-like polypeptide wherein the mature polypeptide comprises the amino acid sequence contained within SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, and optionally further comprises an amino-terminal methionine;

(b) an amino acid sequence for an ortholog of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) an amino acid sequence that is at least about 70, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) a fragment of the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 comprising at least about 25 amino acid residues,

wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(e) an amino acid sequence for an allelic variant or splice variant of either the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, or at least one of (a)-(c) wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

15. An isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(b) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid insertion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(c) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 with at least one amino acid deletion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7;

(d) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7 which has a C- and/or N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

(e) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7, with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

16. An isolated polypeptide encoded by the nucleic acid molecule of Claims 1, 2, or 3.

17. The isolated polypeptide according to Claim 14 wherein the percent identity is determined using a computer program selected from the group consisting of GAP, BLASTP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.

18. An antibody produced by immunizing an animal with a peptide comprising an amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

19. An antibody or fragment thereof that specifically binds the polypeptide of Claims 13, 14, or 15.

20. The antibody of Claim 19 that is a monoclonal antibody.

21. A hybridoma that produces a monoclonal antibody that binds to a peptide comprising an amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

22. A method of detecting or quantitating the amount of C3b/C4b CR-like polypeptide using the anti-C3b/C4b CR-like antibody or fragment of Claims 18, 19, or 20.

23. A selective binding agent or fragment thereof that specifically binds at least one polypeptide wherein said polypeptide comprises the amino acid sequence selected from the group consisting of:

a) the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

b) a fragment of the amino acid sequence set forth in at least one of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7; and

c) a naturally occurring variant of (a) or (b).

24. The selective binding agent of Claim 23 that is an antibody or fragment thereof.

25. The selective binding agent of Claim 23 that is a humanized antibody.

26. The selective binding agent of Claim 23 that is a human antibody or fragment thereof.

27. The selective binding agent of Claim 23 that is a polyclonal antibody or fragment thereof.

28. The selective binding agent Claim 23 that is a monoclonal antibody or fragment thereof.

29. The selective binding agent of Claim 23 that is a chimeric antibody or fragment thereof.

30. The selective binding agent of Claim 23 that is a CDR-grafted antibody or fragment thereof.

31. The selective binding agent of Claim 23 that is an antiidiotypic antibody or fragment thereof.

32. The selective binding agent of Claim 23 which is a variable region fragment.

33. The variable region fragment of Claim 32 which is a Fab or a Fab' fragment.

34. A selective binding agent or fragment thereof comprising at least one complementarity determining region with specificity for a polypeptide having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

35. The selective binding agent of Claim 23 which is bound to a detectable label.

36. The selective binding agent of Claim 23 which antagonizes C3b/C4b CR-like polypeptide biological activity.

37. A method for treating, preventing, or ameliorating a disease, condition, or disorder comprising administering to a patient an effective amount of a selective binding agent according to Claim 23.

38. A selective binding agent produced by immunizing an animal with a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

39. A hybridoma that produces a selective binding agent capable of binding a polypeptide according to Claims 1, 2, or 3.

40. A composition comprising the polypeptide of Claims 13, 14, or 15 and a pharmaceutically acceptable formulation agent.

41. The composition of Claim 40 wherein the pharmaceutically acceptable formulation agent is a carrier, adjuvant, solubilizer, stabilizer, or anti-oxidant.

42. The composition of Claim 40 wherein the polypeptide comprises the mature amino acid sequence portion of SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:7.

43. A polypeptide comprising a derivative of the polypeptide of Claims 13, 14, or 15.

44. The polypeptide of Claim 43 which is covalently modified with a water-soluble polymer.

45. The polypeptide of Claim 44 wherein the water-soluble polymer is selected from the group consisting of polyethylene glycol, monomethoxy-polyethylene glycol, dextran, cellulose, poly-(N-vinyl pyrrolidone)

polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols, and polyvinyl alcohol.

46. A composition comprising a nucleic acid molecule of Claims 1, 2, or 3 and a pharmaceutically acceptable formulation agent.

47. A composition of Claim 46 wherein said nucleic acid molecule is contained in a viral vector.

48. A viral vector comprising a nucleic acid molecule of Claims 1, 2, or 3.

49. A fusion polypeptide comprising the polypeptide of Claims 13, 14, or 15 fused to a heterologous amino acid sequence.

50. The fusion polypeptide of Claim 49 wherein the heterologous amino acid sequence is an IgG constant domain or fragment thereof.

51. A method for treating, preventing or ameliorating a medical condition comprising administering to a patient the polypeptide of Claims 13, 14, or 15 or the polypeptide encoded by the nucleic acid of Claims 1, 2, or 3.

52. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of Claims 13, 14, or 15

or the polypeptide encoded by the nucleic acid molecule of Claims 1, 2, or 3 in a sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

53. A device, comprising:

(a) a membrane suitable for implantation; and

(b) cells encapsulated within said membrane, wherein said cells secrete a protein of Claims 13, 14, or 15, and wherein said membrane is permeable to said protein and impermeable to materials detrimental to said cells.

54. A method of identifying a compound which binds to a polypeptide comprising:

(a) contacting the polypeptide of Claims 13, 14, or 15 with a compound; and

(b) determining the extent of binding of the polypeptide to the compound.

55. A method of modulating levels of a polypeptide in an animal comprising administering to the animal the nucleic acid molecule of Claims 1, 2, or 3.

56. A transgenic non-human mammal comprising the nucleic acid molecule of Claims 1, 2, or 3.

Figure 1A

Map of Human C3b/C4b Complement Receptor like cDNA (SEQ ID NO:1) and Amino Acid Sequences (SEQ ID NO:2)

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   1  CCTGGGGAAGCCTCTCGGTTCCAGGAAAATGGGATGGTTGATTGCCCTAAATTGATTTTT    60
  61  TAAAAGAAAATTCACGAATTGGCAGCCATAGAATAGAGTAATTTCTGTAAAGCACCAGTG   120
 121  ATAGTGATGTTTGAATATTAATATAATGGACCAGAGGCTGTACAGTCTTTGAAAGAGGGT   180
 181  CTTGCTACCTATATATCTAGGGTTTGGCTGTTTAAAGCAGCAAGACCCTCCTTTCAGGTG   240
 241  GAAGTCGATGTACTTGTTGCCTTACCTAAAAGCTTTGACATTTCTCTTTCTTGCAGGCTC   300
 301  ACGGGATCCAGTGTTCCTGACCTCATTGTGAGCATGAGCAACCAGATGTGGCTACATCTG   360
   1                                 M  S  N  Q  M  W  L  H  L     9

 361  CAGTCGGATGATAGCATTGGCTCACCTGGGTTTAAAGCTGTTTACCAAGAAATTGAAAAG   420
  10  Q  S  D  D  S  I  G  S  P  G  F  K  A  V  Y  Q  E  I  E  K    29

 421  GGAGGGTGTGGGGATCCTGGAATCCCCGCCTATGGGAAGCGGACGGGCAGCAGTTTCCTC   480
  30  G  G  C  G  D  P  G  I  P  A  Y  G  K  R  T  G  S  S  F  L    49

 481  CATGGAGATACACTCACCTTTGAATGCCCGGCGGCCTTTGAGCTGGTGGGGGAGAGAGTT   540
  50  H  G  D  T  L  T  F  E  C  P  A  A  F  E  L  V  G  E  R  V    69

 541  ATCACCTGTCAGCAGAACAATCAGTGGTCTGGCAACAAGCCCAGCTGTGTATTTTCATGT   600
  70  I  T  C  Q  Q  N  N  Q  W  S  G  N  K  P  S  C  V  F  S  C    89

 601  TTCTTCAACTTTACGGCATCATCTGGGATTATTCTGTCACCAAATTATCCAGAGGAATAT   660
  90  F  F  N  F  T  A  S  S  G  I  I  L  S  P  N  Y  P  E  E  Y   109

 661  GGGAACAACATGAACTGTGTCTGGTTGATTATCTCGGAGCCAGGAAGTCGAATTCACCTA   720
 110  G  N  N  M  N  C  V  W  L  I  I  S  E  P  G  S  R  I  H  L   129

 721  ATCTTTAATGATTTTGATGTTGAGCCTCAATTTGACTTTCTCGCGGTCAAGGATGATGGC   780
 130  I  F  N  D  F  D  V  E  P  Q  F  D  F  L  A  V  K  D  D  G   149

 781  ATTTCTGACATAACTGTCCTGGGTACTTTTTCTGGCAATGAAGTGCCTTCCCAGCTGGCC   840
 150  I  S  D  I  T  V  L  G  T  F  S  G  N  E  V  P  S  Q  L  A   169

 841  AGCAGTGGGCATATAGTTCGCTTGGAATTTCAGTCTGACCATTCCACTACTGGCAGAGGG   900
 170  S  S  G  H  I  V  R  L  E  F  Q  S  D  H  S  T  T  G  R  G   189

 901  TTCAACATCACTTACACCACATTTGGTCAGAATGAGTGCCATGATCCTGGCATTCCTATA   960
 190  F  N  I  T  Y  T  T  F  G  Q  N  E  C  H  D  P  G  I  P  I   209

 961  AACGGACGACGTTTTGGTGACAGGTTTCTACTCGGGAGCTCGGTTTCTTTCCACTGTGAT  1020
 210  N  G  R  R  F  G  D  R  F  L  L  G  S  S  V  S  F  H  C  D   229

1021  GATGGCTTTGTCAAGACCCAGGGATCCGAGTCCATTACCTGCATACTGCAAGACGGGAAC  1080
 230  D  G  F  V  K  T  Q  G  S  E  S  I  T  C  I  L  Q  D  G  N   249

1081  GTGGTCTGGAGCTCCACCGTGCCCCGCTGTGAAGCTCCATGTGGTGGACATCTGACAGCG  1140
 250  V  V  W  S  S  T  V  P  R  C  E  A  P  C  G  G  H  L  T  A   269

1141  TCCAGCGGAGTCATTTTGCCTCCTGGATGGCCAGGATATTATAAGGATTCTTTACATTGT  1200
 270  S  S  G  V  I  L  P  P  G  W  P  G  Y  Y  K  D  S  L  H  C   289

1201  GAATGGATAATTGAAGCAAAACCAGGCCACTCTATCAAAATAACTTTTGACAGATTTCAG  1260
 290  E  W  I  I  E  A  K  P  G  H  S  I  K  I  T  F  D  R  F  Q   309
```

Figure 1B

```
1261 ACAGAGGTCAATTATGACACCTTGGAGGTCAGAGATGGGCCAGCCAGTTCGTCCCCACTG 1320
310  T  E  V  N  Y  D  T  L  E  V  R  D  G  P  A  S  S  S  P  L  329

1321 ATCGGCGAGTACCACGGCACCCAGGCACCCCAGTTCCTCATCAGCACCGGGAACTTCATG 1380
330  I  G  E  Y  H  G  T  Q  A  P  Q  F  L  I  S  T  G  N  F  M  349

1381 TACCTGCTATTCACCACTGACAACAGCCGCTCCAGCATCGGCTTCCTCATCCACTATGAG 1440
350  Y  L  L  F  T  T  D  N  S  R  S  S  I  G  F  L  I  H  Y  E  369

1441 AGTGTGACGCTTGAGTCGGATTCCTGCCTGGACCCGGGCATCCCTGTGAACGRCCATCGC 1500
370  S  V  T  L  E  S  D  S  C  L  D  P  G  I  P  V  N  X  H  R  389

1501 CACGGTGGAGACTTTGGCATCAGGTCCACAGTGACTTTCAGCTGTGACCCGGGGTACACA 1560
390  H  G  G  D  F  G  I  R  S  T  V  T  F  S  C  D  P  G  Y  T  409

1561 CTAAGTGACGACGAGCCCCTCGTCTGTGAGAGGAACCACCAGTGGAACCACGCCTTGCCC 1620
410  L  S  D  D  E  P  L  V  C  E  R  N  H  Q  W  N  H  A  L  P  429

1621 AGCTGCGACGCTCTATGTGGAGGCTACATCCAAGGGAAGAGTGGAACAGTCCTTTCTCCT 1680
430  S  C  D  A  L  C  G  G  Y  I  Q  G  K  S  G  T  V  L  S  P  449

1681 GGGTTTCCAGATTTTTATCCAAACTCTCTAAACYGCACGTGGACCATTGAAGTGTCTCAT 1740
450  G  F  P  D  F  Y  P  N  S  L  N  X  T  W  T  I  E  V  S  H  469

1741 GGGAAAGGAGTTCAAATGATCTTTCACACCTTTCATCTTGAGAGTTCCCACGACTATTTA 1800
470  G  K  G  V  Q  M  I  F  H  T  F  H  L  E  S  S  H  D  Y  L  489

1801 CTGATCACAGAGGATGGAAGTTTTTCCGAGCCCGTTGCCAGGCTCACCGGGTCGGTGTTG 1860
490  L  I  T  E  D  G  S  F  S  E  P  V  A  R  L  T  G  S  V  L  509

1861 CCTCATACGATCAAGGCAGGCCTGTTTGGAAACTTCACTGCCCAGCTTCGGTTTATATCA 1920
510  P  H  T  I  K  A  G  L  F  G  N  F  T  A  Q  L  R  F  I  S  529

1921 GACTTCTCAATTTCGTACGAGGGCTTCAATATCACATTTTCAGAATATGACCTGGAGCCA 1980
530  D  F  S  I  S  Y  E  G  F  N  I  T  F  S  E  Y  D  L  E  P  549

1981 TGTGATGATCCTGGAGTCCCTGCCTTCAGCCGAAGAATTGGTTTTCACTTTGGTGTGGGA 2040
550  C  D  D  P  G  V  P  A  F  S  R  R  I  G  F  H  F  G  V  G  569

2041 GACTCTCTGACGTTTTCCTGCTTCCTGGGATATCGTTTAGAAGGTGCCRCCAAGCTTACC 2100
570  D  S  L  T  F  S  C  F  L  G  Y  R  L  E  G  A  X  K  L  T  589

2101 TGCCTGGGTGGGGGCCGCCGTGTGTGGAGTGCACCTCTGCCAAGGTGTGTGGCCGAATGT 2160
590  C  L  G  G  G  R  R  V  W  S  A  P  L  P  R  C  V  A  E  C  609

2161 GGAGCAAGTGTCAAAGGAAATGAAGGAACATTACTGTCTCCAAATTTTCCATCCAATTAT 2220
610  G  A  S  V  K  G  N  E  G  T  L  L  S  P  N  F  P  S  N  Y  629

2221 GATAATAACCATGAGTGTATCTATAAAATAGAAACAGAAGCCGGCAAGGGCATCCACCTT 2280
630  D  N  N  H  E  C  I  Y  K  I  E  T  E  A  G  K  G  I  H  L  649

2281 AGAACACGAAGCTTCCAGCTGTTTGAAGGAGATACTCTAAAGGTATATGATGGAAAAGAC 2340
650  R  T  R  S  F  Q  L  F  E  G  D  T  L  K  V  Y  D  G  K  D  669

2341 AGTTCCTCACGTCCACTGGGCACGTTCACTAAAAATGAACTTCTGGGGCTGATCCTAAAC 2400
670  S  S  S  R  P  L  G  T  F  T  K  N  E  L  L  G  L  I  L  N  689
```

Figure 1C

```
2401  AGCACATCCAATCACCTRTGGCTAGAGTTCAACACCAATGGATCTGACACCGACCAAGGT  2460
690   S  T  S  N  H  L  W  L  E  F  N  T  N  G  S  D  T  D  Q  G   709

2461  TTTCAACTCACCTATACCAGTTTTGATCTGGTAAAATGTGAGGATCCGGGCATCCCTAAC  2520
710   F  Q  L  T  Y  T  S  F  D  L  V  K  C  E  D  P  G  I  P  N   729

2521  TACGGCTATAGGATCCGTGATGAAGGCCACTTTACCGACACTGTAGTTCTGTACAGTTGC  2580
730   Y  G  Y  R  I  R  D  E  G  H  F  T  D  T  V  V  L  Y  S  C   749

2581  AACCCGGGGTACGCCATGCATGGCAGCAACACCCTGACCTGTTTGAGTGGAGACAGGAGA  2640
750   N  P  G  Y  A  M  H  G  S  N  T  L  T  C  L  S  G  D  R  R   769

2641  GTGTGGGACAAACCACTACCTTCGTGCATAGCGGAATGTGGTGGTCAGATCCATGCAGCC  2700
770   V  W  D  K  P  L  P  S  C  I  A  E  C  G  G  Q  I  H  A  A   789

2701  ACATCAGGACGAATATTGTCCCCTGGCTATCCAGCTCCGTATGACAACAACCTCCACTGC  2760
790   T  S  G  R  I  L  S  P  G  Y  P  A  P  Y  D  N  N  L  H  C   809

2761  ACCTGGATTATAGAGGCAGACCCAGGAAAGACCATTAGCCTCCATTTCATTGTTTTCGAC  2820
810   T  W  I  I  E  A  D  P  G  K  T  I  S  L  H  F  I  V  F  D   829

2821  ACGGAGATGGCTCACGACATCCTCAAGGTCTGGGACGGGCCGGTGGACAGTGACATCCTG  2880
830   T  E  M  A  H  D  I  L  K  V  W  D  G  P  V  D  S  D  I  L   849

2881  CTGAAGGAGTGGAGTGGCTCCGCCCTTCCGGAGGACATCCACAGCACCTTCAACTCACTC  2940
850   L  K  E  W  S  G  S  A  L  P  E  D  I  H  S  T  F  N  S  L   869

2941  ACCCTGCAGTTCGACAGCGACTTCTTCATCAGCAAGTCTGGCTTCTCCATCCAGTTCTCC  3000
870   T  L  Q  F  D  S  D  F  F  I  S  K  S  G  F  S  I  Q  F  S   889

3001  ACCTCAATTGCAGCCACCTGTAACGATCCAGGTATGCCCCAAAATGGCACCCGCTATGGA  3060
890   T  S  I  A  A  T  C  N  D  P  G  M  P  Q  N  G  T  R  Y  G   909

3061  GACAGCAGAGAGGCTGGAGACACCGTCACATTCCAGTGTGACCCTGGCTATCAGCTCCAA  3120
910   D  S  R  E  A  G  D  T  V  T  F  Q  C  D  P  G  Y  Q  L  Q   929

3121  GGACAAGCCAAAATCACCTGTGTGCAGCTGAATAACCGGTTCTTTTGGCAACCAGACCCT  3180
930   G  Q  A  K  I  T  C  V  Q  L  N  N  R  F  F  W  Q  P  D  P   949

3181  CCTACATGCATAGCTGCTTGTGGAGGGAATCTGACGGGCCCAGCAGGTGTTATTTTGTCA  3240
950   P  T  C  I  A  A  C  G  G  N  L  T  G  P  A  G  V  I  L  S   969

3241  CCCAACTACCCACAGCCGTATCCTCCTGGGAAGGAATGTGACTGGAGAGTAAAAGTGAAC  3300
970   P  N  Y  P  Q  P  Y  P  P  G  K  E  C  D  W  R  V  K  V  N   989

3301  CCGGACTTTGTCATCGCCTTGATATTCAAAAGTTTCAACATGGAGCCCAGCTATGACTTC  3360
990   P  D  F  V  I  A  L  I  F  K  S  F  N  M  E  P  S  Y  D  F  1009

3361  CTACACATCTATGAAGGGGAAGATTCCAACAGCCCCCTCATTGGGAGTTACCAGGGCTCT  3420
1010  L  H  I  Y  E  G  E  D  S  N  S  P  L  I  G  S  Y  Q  G  S  1029

3421  CAGGCCCCAGAAAGAATAGAGAGTAGCGGAAACAGCCTGTTTCTGGCATTTCGGAGTGAT  3480
1030  Q  A  P  E  R  I  E  S  S  G  N  S  L  F  L  A  F  R  S  D  1049

3481  GCCTCCGTGGGCCTTTCAGGGTTCGCCATTGAATTTAAAGAGAAACCACGGGAAGCTTGT  3540
1050  A  S  V  G  L  S  G  F  A  I  E  F  K  E  K  P  R  E  A  C  1069
```

Figure 1D

```
3541  TTTGACCCAGGAAATATAATGAATGGGACAAGAGTTGGAACAGACTTCAAGCTTGGCTCC  3600
1070  F  D  P  G  N  I  M  N  G  T  R  V  G  T  D  F  K  L  G  S   1089

3601  ACCATCACCTACCAGTGTGACTCTGGCTATAAGATTCTTGACCCCTCATCCATCACCTGT  3660
1090  T  I  T  Y  Q  C  D  S  G  Y  K  I  L  D  P  S  S  I  T  C   1109

3661  GTGATTGGGGCTGATGGGAAACCCTCCTGGGACCAAGTGCTGCCCTCCTGCAATGCTCCC  3720
1110  V  I  G  A  D  G  K  P  S  W  D  Q  V  L  P  S  C  N  A  P   1129

3721  TGTGGAGGCCAGTACACGGGATCAGAAGGGGTAGTTTTATCACCAAACTACCCCCATAAT  3780
1130  C  G  G  Q  Y  T  G  S  E  G  V  V  L  S  P  N  Y  P  H  N   1149

3781  TACACAGCTGGTCAAATATGCCTCTATTCCATCACGGTACCAAAGGAATTCGTGGTCTTT  3840
1150  Y  T  A  G  Q  I  C  L  Y  S  I  T  V  P  K  E  F  V  V  F   1169

3841  GGACAGTTTGCCTATTTCCAGACAGCCCTGAATGATTTGGCAGAATTATTTGATGGAACC  3900
1170  G  Q  F  A  Y  F  Q  T  A  L  N  D  L  A  E  L  F  D  G  T   1189

3901  CATGCACAGGCCAGACTTCTCAGCTCACTCTCGGGGTCTCACTCAGGGGAAACATTGCCC  3960
1190  H  A  Q  A  R  L  L  S  S  L  S  G  S  H  S  G  E  T  L  P   1209

3961  TTGGCTACGTCAAATCAAATTCTGCTCCGATTCAGTGCAAAGAGCGGTGCCTCTGCCCGC  4020
1210  L  A  T  S  N  Q  I  L  L  R  F  S  A  K  S  G  A  S  A  R   1229

4021  GGCTTCCACTTCGTGTATCAAGCTGTTCCTCGTACCAGTGACACCCAATGCAGCTCTGTC  4080
1230  G  F  H  F  V  Y  Q  A  V  P  R  T  S  D  T  Q  C  S  S  V   1249

4081  CCCGAGCCCAGATACGGAAGGAGAATTGGTTCTGAGTTTTCTGCCGGCTCCATCGTCCGA  4140
1250  P  E  P  R  Y  G  R  R  I  G  S  E  F  S  A  G  S  I  V  R   1269

4141  TTCGAGTRCAACCCGGGATACCTGCTTCAGGGTTCCACGGCGCTCCACTGCCAGTCCGTG  4200
1270  F  E  X  N  P  G  Y  L  L  Q  G  S  T  A  L  H  C  Q  S  V   1289

4201  CCCAACGCCTTGGCACAGTGGAACGACACGATCCCCAGCTGTGTGGTACCCTGCAGTGGC  4260
1290  P  N  A  L  A  Q  W  N  D  T  I  P  S  C  V  V  P  C  S  G   1309

4261  AATTTCACTCAACGAAGAGGTACAATCCTGTCCCCCGGCTACCCTGAGCCATACGGAAAC  4320
1310  N  F  T  Q  R  R  G  T  I  L  S  P  G  Y  P  E  P  Y  G  N   1329

4321  AACTTGAACTGTATATGGAAGATCATAGTTACGGAGGGCTCGGGAATTCAGATCCAAGTG  4380
1330  N  L  N  C  I  W  K  I  I  V  T  E  G  S  G  I  Q  I  Q  V   1349

4381  ATCAGTTTTGCCACGGAGCAGAACTGGGACTCCCTTGAGATCCACGATGGTGGGGATGTG  4440
1350  I  S  F  A  T  E  Q  N  W  D  S  L  E  I  H  D  G  G  D  V   1369

4441  ACCGCACCCAGACTGGGAAGCTTCTCAGGCACCACAGTACCGGCACTGCTGAACAGTACT  4500
1370  T  A  P  R  L  G  S  F  S  G  T  T  V  P  A  L  L  N  S  T   1389

4501  TCCAACCAACTCTACCTGCATTTCCAGTCTGACATTAGTGTGGCAGCTGCTGGTTTCCAC  4560
1390  S  N  Q  L  Y  L  H  F  Q  S  D  I  S  V  A  A  A  G  F  H   1409

4561  CTGGAATACAAAACTGTAGGTCTTGCTGCATGCCAAGAACCAGCCCTCCCCAGCAACAGC  4620
1410  L  E  Y  K  T  V  G  L  A  A  C  Q  E  P  A  L  P  S  N  S   1429

4621  ATCAAAATCGGAGATCGGTACATGGTGAACGACGTGCTCTCCTTCCAGTGCGAGCCCGGG  4680
1430  I  K  I  G  D  R  Y  M  V  N  D  V  L  S  F  Q  C  E  P  G   1449
```

Figure 1E

```
4681  TACACCCTGCAGGGCCGTTCCCACATTTCCTGTATGCCAGGGACCGTTCGCCGTTGGAAC  4740
1450  Y  T  L  Q  G  R  S  H  I  S  C  M  P  G  T  V  R  R  W  N   1469

4741  TATCCGTCTCCCCTGTGCATTGCAACCTGTGGAGGGACGCTGAGCACCTTGGGTGGTGTG  4800
1470  Y  P  S  P  L  C  I  A  T  C  G  G  T  L  S  T  L  G  G  V   1489

4801  ATCCTGAGCCCCGGCTTCCCAGGTTCTTACCCCAACAACTTAGACTGCACCTGGAGGATC  4860
1490  I  L  S  P  G  F  P  G  S  Y  P  N  N  L  D  C  T  W  R  I   1509

4861  TCATTACCCATCGGCTATGGTGCACATATTCAGTTTCTGAATTTTTCTACCGAAGCTAAT  4920
1510  S  L  P  I  G  Y  G  A  H  I  Q  F  L  N  F  S  T  E  A  N   1529

4921  CATGACTTCCTTGAAATTCAAAATGGACCTTACCACACCAGCCCCATGATTGGACAATTT  4980
1530  H  D  F  L  E  I  Q  N  G  P  Y  H  T  S  P  M  I  G  Q  F   1549

4981  AGCGGCACGGATCTCCCCGCGGCCCTGCTGAGCACAACGCATGAAACCCTCATCCACTTT  5040
1550  S  G  T  D  L  P  A  A  L  L  S  T  T  H  E  T  L  I  H  F   1569

5041  TATAGTGACCATTCGCAAAACCGGCAAGGATTTAAACTTGCTTACCAAGCCTATGAATTA  5100
1570  Y  S  D  H  S  Q  N  R  Q  G  F  K  L  A  Y  Q  A  Y  E  L   1589

5101  CAGAACTGTCCAGATCCACCCCCATTTCAGAATGGGTACATGATCAACTCGGATTACAGC  5160
1590  Q  N  C  P  D  P  P  P  F  Q  N  G  Y  M  I  N  S  D  Y  S   1609

5161  GTGGGGCAATCAGTATCTTTCGAGTGTTATCCTGGGTACATTCTAATAGGCCATCCTGTC  5220
1610  V  G  Q  S  V  S  F  E  C  Y  P  G  Y  I  L  I  G  H  P  V   1629

5221  CTCACTTGTCAGCATGGGATCAACAGAAACTGGAACTACCCTTTTCCAAGATGTGATGCC  5280
1630  L  T  C  Q  H  G  I  N  R  N  W  N  Y  P  F  P  R  C  D  A   1649

5281  CCTTGTGGGTACAACGTAACTTCTCAGAACGGCACCATCTACTCCCCTGGCTTTCCTGAT  5340
1650  P  C  G  Y  N  V  T  S  Q  N  G  T  I  Y  S  P  G  F  P  D   1669

5341  GAGTATCCGATCCTGAAGGACTGCATTTGGCTCATCACGGTGCCTCCAGGGCACGGAGTT  5400
1670  E  Y  P  I  L  K  D  C  I  W  L  I  T  V  P  P  G  H  G  V   1689

5401  TACATCAACTTCACCCTGTTACAGACGGAAGCTGTCAACGATTACATTGCTGTTTGGGAC  5460
1690  Y  I  N  F  T  L  L  Q  T  E  A  V  N  D  Y  I  A  V  W  D   1709

5461  GGTCCCGATCAGAACTCACCCCAGCTGGGAGTTTTCAGTGGCAACACAGCCCTCGAAACG  5520
1710  G  P  D  Q  N  S  P  Q  L  G  V  F  S  G  N  T  A  L  E  T   1729

5521  GCGTATAGCTCCACCAACCAAGTCCTGCTCAAGTTCCACAGCGACTTTTCAAATGGAGGC  5580
1730  A  Y  S  S  T  N  Q  V  L  L  K  F  H  S  D  F  S  N  G  G   1749

5581  TTCTTTGTCCTCAATTTCCACGCATTTCAGCTCAAGAAATGTCAACCTCCCCCAGCGGTT  5640
1750  F  F  V  L  N  F  H  A  F  Q  L  K  K  C  Q  P  P  P  A  V   1769

5641  CCACAGGCAGAAATGCTTACTGAGGATGATGATTTCGAGATAGGAGATTTTGTGAAGTAC  5700
1770  P  Q  A  E  M  L  T  E  D  D  D  F  E  I  G  D  F  V  K  Y   1789

5701  CAGTGCCACCCCGGGTACACCTTGGTGGGGACCGACATTCTGACTTGCAAGCTCAGTTCC  5760
1790  Q  C  H  P  G  Y  T  L  V  G  T  D  I  L  T  C  K  L  S  S   1809

5761  CAGTTGCAGTTTGAGGGTTCTCTCCCAACATGTGAAGCACAATGCCCAGCAAATGAAGTC  5820
1810  Q  L  Q  F  E  G  S  L  P  T  C  E  A  Q  C  P  A  N  E  V   1829
```

Figure 1F

```
5821  CGGACTGGATCATCGGGAGTCATTCTCAGTCCAGGGTATCCGGGTAATTATTTTAACTCC  5880
1830  R  T  G  S  S  G  V  I  L  S  P  G  Y  P  G  N  Y  F  N  S   1849

5881  CAGACTTGCTCTTGGAGTATTAAAGTGGAACCAAACTACAACATTACCATCTTTGTGGAC  5940
1850  Q  T  C  S  W  S  I  K  V  E  P  N  Y  N  I  T  I  F  V  D   1869

5941  ACATTTCAAAGTGAAAAGCAGTTTGATGCACTGGAAGTGTTTGATGGTTCTTCTGGGCAA  6000
1870  T  F  Q  S  E  K  Q  F  D  A  L  E  V  F  D  G  S  S  G  Q   1889

6001  AGTCCTCTGCTAGTAGTCTTAAGTGGGAATCATACTGAACAATCAAATTTTACAAGCAGG  6060
1890  S  P  L  L  V  V  L  S  G  N  H  T  E  Q  S  N  F  T  S  R   1909

6061  AGTAATCAGTTATATCTCCGCTGGTCCACTGACCATGCCACCAGTAAGAAAGGATTCAAG  6120
1910  S  N  Q  L  Y  L  R  W  S  T  D  H  A  T  S  K  K  G  F  K   1929

6121  ATTCGCTATGCAGCACCTTACTGCAGTTTGACCCACCCCCTGAAGAATGGGGGTATTCTA  6180
1930  I  R  Y  A  A  P  Y  C  S  L  T  H  P  L  K  N  G  G  I  L   1949

6181  AACAGGACTGCAGGAGCGGTTGGAAGCAAAGTGCATTATTTTTGCAAGCCTGGATACCGA  6240
1950  N  R  T  A  G  A  V  G  S  K  V  H  Y  F  C  K  P  G  Y  R   1969

6241  ATGGTCGGCCACAGCAATGCAACCTGTAGACGAAACCCACTTGGCATGTACCAGTGGGAC  6300
1970  M  V  G  H  S  N  A  T  C  R  R  N  P  L  G  M  Y  Q  W  D   1989

6301  TCCCTCACGCCACTCTGCCAGGCTGTGTCCTGTGGAATCCCAGAATCCCCAGGAAACGGT  6360
1990  S  L  T  P  L  C  Q  A  V  S  C  G  I  P  E  S  P  G  N  G   2009

6361  TCATTTACCGGGAACGAGTTCACTTTGGACAGTAAAGTGGTCTATGAATGTCATGAGGGC  6420
2010  S  F  T  G  N  E  F  T  L  D  S  K  V  V  Y  E  C  H  E  G   2029

6421  TTCAAGCTTGAATCCAGCCAGCAAGCAACAGCCGTGTGTCAAGAAGATGGGCTGTGGAGT  6480
2030  F  K  L  E  S  S  Q  Q  A  T  A  V  C  Q  E  D  G  L  W  S   2049

6481  AACAAGGGGAAGCCGCCCACGTGTAAGCCGGTCGCTTGCCCCAGCATTGAAGCTCAGCTC  6540
2050  N  K  G  K  P  P  T  C  K  P  V  A  C  P  S  I  E  A  Q  L   2069

6541  TCAGAACATGTCATCTGGAGGCTGGTTTCAGGATCCTTGAATGAGTACGGTGCTCAAGTA  6600
2070  S  E  H  V  I  W  R  L  V  S  G  S  L  N  E  Y  G  A  Q  V   2089

6601  TTGCTGAGCTGCAGTCCTGGTTACTACTTAGAAGGCTGGAGGCTCCTGCGGTGCCAGGCC  6660
2090  L  L  S  C  S  P  G  Y  Y  L  E  G  W  R  L  L  R  C  Q  A   2109

6661  AATGGGACGTGGAACATAGGAGATGAGAGGCCAAGCTGTCGAGTTATCTCGTGTGGAAGC  6720
2110  N  G  T  W  N  I  G  D  E  R  P  S  C  R  V  I  S  C  G  S   2129

6721  CTTTCCTTTCCCCCAAATGGCAACAAGATTGGAACGTTGACAGTTTATGGGGCCACAGCT  6780
2130  L  S  F  P  P  N  G  N  K  I  G  T  L  T  V  Y  G  A  T  A   2149

6781  ATATTTACGTGCAACACCGGCTACACGCTTGTGGGGTCTCATGTCAGAGAGTGCTTGGCA  6840
2150  I  F  T  C  N  T  G  Y  T  L  V  G  S  H  V  R  E  C  L  A   2169

6841  AATGGGCTCTGGAGCGGCAGCGAAACTCGATGTCTGGCTGGCCACTGCGGTTCCCCAGAC  6900
2170  N  G  L  W  S  G  S  E  T  R  C  L  A  G  H  C  G  S  P  D   2189

6901  CCGATTGTGAACGGTCACATTAGTGGAGATGGCTTCAGTTACAGAGACACGGTGGTTTAC  6960
2190  P  I  V  N  G  H  I  S  G  D  G  F  S  Y  R  D  T  V  V  Y   2209
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Figure 1G

```
6961 CAGTGCAATCCTGGTTTCCGGCTTGTGGGAACTTCCGTGAGGATATGCCTGCAAGACCAC 7020
2210 Q   C   N   P   G   F   R   L   V   G   T   S   V   R   I   C   L   Q   D   H    2229

7021 AAGTGGTCTGGACAAACGCCTGTCTGTGTCCCCATCACATGTGGTCACCCTGGAAACCCT 7080
2230 K   W   S   G   Q   T   P   V   C   V   P   I   T   C   G   H   P   G   N   P    2249

7081 GCCCACGGATTCACTAATGGCAGTGAGTTCAACCTGAATGATGTCGTGAATTTCACCTGC 7140
2250 A   H   G   F   T   N   G   S   E   F   N   L   N   D   V   V   N   F   T   C    2269

7141 AACACGGGCTATTTGCTGCAGGGCGTGTCTCGAGCCCAGTGTCGGAGCAACGGCCAGTGG 7200
2270 N   T   G   Y   L   L   Q   G   V   S   R   A   Q   C   R   S   N   G   Q   W    2289

7201 AGTAGCCCTCTGCCCACGTGTCGAGTGGTGAACTGTTCTGATCCAGGCTTTGTGGAAAAT 7260
2290 S   S   P   L   P   T   C   R   V   V   N   C   S   D   P   G   F   V   E   N    2309

7261 GCCATTCGTCACGGGCAACAGAACTTCCCTGAGAGTTTTGAGTATGGAATGAGTATCCTG 7320
2310 A   I   R   H   G   Q   Q   N   F   P   E   S   F   E   Y   G   M   S   I   L    2329

7321 TACCATTGCAAGAAGGGATTTTACTTGCTGGGATCTTCAGCCTTGACCTGTATGGCAAAT 7380
2330 Y   H   C   K   K   G   F   Y   L   L   G   S   S   A   L   T   C   M   A   N    2349

7381 GGCTTATGGGACCGATCCCTGCCCAAGTGTTTGGCTATATCGTGTGGACACCCAGGGGTC 7440
2350 G   L   W   D   R   S   L   P   K   C   L   A   I   S   C   G   H   P   G   V    2369

7441 CCTGCCAACGCCGTCCTCACTGGAGAGCTGTTTACCTATGGCGCCGTCGTGCACTACTCC 7500
2370 P   A   N   A   V   L   T   G   E   L   F   T   Y   G   A   V   V   H   Y   S    2389

7501 TGCAGAGGGAGCGAGAGCCTCATAGGCAACGACACGAGAGTGTGCCAGGAAGACAGTCAC 7560
2390 C   R   G   S   E   S   L   I   G   N   D   T   R   V   C   Q   E   D   S   H    2409

7561 TGGAGCGGGGCACTGCCCCACTGCACAGGAAATAATCCTGGATTCTGTGGTGATCCGGGG 7620
2410 W   S   G   A   L   P   H   C   T   G   N   N   P   G   F   C   G   D   P   G    2429

7621 ACCCCAGCACATGGGTCTCGGCTTGGTGATGACTTTAAGACAAAGAGTCTTCTCCGCTTC 7680
2430 T   P   A   H   G   S   R   L   G   D   D   F   K   T   K   S   L   L   R   F    2449

7681 TCCTGTGAAATGGGGCACCAGCTGAGGGGCTCCCCTGAACGCACGTGTTTGCTCAATGGG 7740
2450 S   C   E   M   G   H   Q   L   R   G   S   P   E   R   T   C   L   L   N   G    2469

7741 TCATGGTCAGGACTGCAGCCGGTGTGTGAGGCCGTGTCCTGTGGCAACCCTGGCACACCC 7800
2470 S   W   S   G   L   Q   P   V   C   E   A   V   S   C   G   N   P   G   T   P    2489

7801 ACCAACGGAATGATTGTCAGTAGTGATGGCATTCTGTTCTCCAGCTCGGTCATCTATGCC 7860
2490 T   N   G   M   I   V   S   S   D   G   I   L   F   S   S   S   V   I   Y   A    2509

7861 TGCTGGGAAGGCTACAAGACCTCAGGGCTCATGACACGGCATTGCACAGCCAATGGGACC 7920
2510 C   W   E   G   Y   K   T   S   G   L   M   T   R   H   C   T   A   N   G   T    2529

7921 TGGACAGGCACTGCTCCCGACTGCACAATTATAAGTTGTGGGGATCCAGGCACACTAGCA 7980
2530 W   T   G   T   A   P   D   C   T   I   I   S   C   G   D   P   G   T   L   A    2549

7981 AATGGCATCCAGTTTGGGACCGACTTCACCTTCAACAAGACTGTGAGCTATCAGTGTAAC 8040
2550 N   G   I   Q   F   G   T   D   F   T   F   N   K   T   V   S   Y   Q   C   N    2569
```

Figure 1H

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8041  CCAGGCTATGTCATGGAAGCAGTCACATCCGCCACTATTCGCTGTACCAAAGACGGCAGG  8100
2570  P   G   Y   V   M   E   A   V   T   S   A   T   I   R   C   T   K   D   G   R   2589

8101  TGGAATCCGAGCAAACCTGTCTGCAAAGCCGTGCTGTGTCCTCAGCCGCCGCCGGTGCAG  8160
2590  W   N   P   S   K   P   V   C   K   A   V   L   C   P   Q   P   P   P   V   Q   2609

8161  AATGGAACAGTGGAGGGAAGTGATTTCCGCTGGGGCTCCAGCATAAGTTACAGCTGCATG  8220
2610  N   G   T   V   E   G   S   D   F   R   W   G   S   S   I   S   Y   S   C   M   2629

8221  GACGGTTACCAGCTCTCTCACTCCGCCATCCTCTCCTGTGAAGGTCGCGGGGTGTGGAAA  8280
2630  D   G   Y   Q   L   S   H   S   A   I   L   S   C   E   G   R   G   V   W   K   2649

8281  GGAGAGATCCCCCAGTGTCTCCCTGTGTTCTGCGGAGACCCTGGCATCCCCGCAGAAGGG  8340
2650  G   E   I   P   Q   C   L   P   V   F   C   G   D   P   G   I   P   A   E   G   2669

8341  CGACTTAGTGGGAAAAGTTTCACCTATAAGTCCGAAGTCTTCTTCCAGTGCAAATCTCCA  8400
2670  R   L   S   G   K   S   F   T   Y   K   S   E   V   F   F   Q   C   K   S   P   2689

8401  TTTATACTCGTGGGATCCTCCAGAAGAGTCTGCCAAGCTGACGGCACGTGGAGCGGCATA  8460
2690  F   I   L   V   G   S   S   R   R   V   C   Q   A   D   G   T   W   S   G   I   2709

8461  CAACCCACCTGCATTGATCCTGCTCATAACACCTGCCCAGACCCTGGTACGCCACACTTT  8520
2710  Q   P   T   C   I   D   P   A   H   N   T   C   P   D   P   G   T   P   H   F   2729

8521  GGAATACAGAATAGCTCCAGAGGCTATGAGGTTGGAAGCACGGTTTTTTTCAGGTGCAGA  8580
2730  G   I   Q   N   S   S   R   G   Y   E   V   G   S   T   V   F   F   R   C   R   2749

8581  AAAGGCTACCATATTCAAGGTTCCACGACTCGCACCTGCCTTGCCAATTTAACATGGAGT  8640
2750  K   G   Y   H   I   Q   G   S   T   T   R   T   C   L   A   N   L   T   W   S   2769

8641  GGGATACAGACCGAATGTATACCTCATGCCTGCAGACAGCCAGAAACCCCGGCACACGCG  8700
2770  G   I   Q   T   E   C   I   P   H   A   C   R   Q   P   E   T   P   A   H   A   2789

8701  GATGTGAGAGCCATCGATCTTCCTACTTTCGGCTACACCTTAGTGTACACCTGCCATCCA  8760
2790  D   V   R   A   I   D   L   P   T   F   G   Y   T   L   V   Y   T   C   H   P   2809

8761  GGCTTTTTCCTCGCAGGGGGATCTGAGCACAGAACATGTAAAGCAGACATGAAATGGACA  8820
2810  G   F   F   L   A   G   G   S   E   H   R   T   C   K   A   D   M   K   W   T   2829

8821  GGAAAGTCGCCTGTGTGTAAAAGTAAAGGAGTGAGAGAAGTTAATGAAACAGTTACTAAA  8880
2830  G   K   S   P   V   C   K   S   K   G   V   R   E   V   N   E   T   V   T   K   2849

8881  ACTCCAGTTCCTTCAGATGTCTTTTTCGTCAATTCACTGTGGAAGGGGTATTATGAATAT  8940
2850  T   P   V   P   S   D   V   F   F   V   N   S   L   W   K   G   Y   Y   E   Y   2869

8941  TTAGGGAAAAGACAACCCGCCACTCTAACTGTTGACTGGTTCAATGCAACAAGCAGTAAG  9000
2870  L   G   K   R   Q   P   A   T   L   T   V   D   W   F   N   A   T   S   S   K   2889

9001  GTGAATGCCACCTTCAGCGAAGCCTCGCCAGTGGAGCTGAAGTTGACAGGCATTTACAAG  9060
2890  V   N   A   T   F   S   E   A   S   P   V   E   L   K   L   T   G   I   Y   K   2909

9061  AAGGAGGAGGCCCACTTACTCCTGAAAGCTTTTCAAATTAAAGGCCAGGCAGATATTTTT  9120
2910  K   E   E   A   H   L   L   L   K   A   F   Q   I   K   G   Q   A   D   I   F   2929

9121  GTAAGCAAGTTCGAAAATGACAACTGGGGACTAGATGGTTATGTGTCATCTGGACTTGAA  9180
2930  V   S   K   F   E   N   D   N   W   G   L   D   G   Y   V   S   S   G   L   E   2949
```

Figure 1I

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9181  AGAGGAGGATTTACTTTTCAAGGTGACATTCATGGAAAAGACTTTGGAAAATTTAAGCTA  9240
2950  R  G  G  F  T  F  Q  G  D  I  H  G  K  D  F  G  K  F  K  L   2969

9241  GAAAGGCAAGATCCTTTAAACCCAGATCAAGACTCTTCCAGTCATTACCACGGCACCAGC  9300
2970  E  R  Q  D  P  L  N  P  D  Q  D  S  S  S  H  Y  H  G  T  S   2989

9301  AGTGGCTCTGTGGCGGCTGCCATTCTGGTTCCTTTCTTTGCTCTAATTTTATCAGGGTTT  9360
2990  S  G  S  V  A  A  A  I  L  V  P  F  F  A  L  I  L  S  G  F

9361  GCATTTTACCTCTACAAACACAGAACGAGACCAAAAGTTCAATACAATGGCTATGCTGGG  9420
3010  A  F  Y  L  Y  K  H  R  T  R  P  K  V  Q  Y  N  G  Y  A  G   3029

9421  CATGAAAACAGCAATGGACAAGCATCGTTTGAAAACCCCATGTATGATACAAACTTAAAA  9480
3030  H  E  N  S  N  G  Q  A  S  F  E  N  P  M  Y  D  T  N  L  K   3049

9481  CCCACAGAAGCCAAGGCTGTGAGGTTTGACACAACTCTGAACACAGTCTGTACAGTGGTA  9540
3050  P  T  E  A  K  A  V  R  F  D  T  T  L  N  T  V  C  T  V  V   3069

9541  TAGCCCTCAGTGCCCCAACAGGACTGATTCATAGCCATACCTCTGATGGACAAGCAGTGA  9600
3070  *                                                             3070
9601  TTCCTTTGGTGCCATATACCACTCTCCCYTCCACTCTGGCTTTACTGCAGCGATCTTCAA  9660
9661  CCTTGTCTACTGGCATAAGTGCAGCGGGGATCTCTACTCAAATGTGTCAGGGTCTTCTAC  9720
9721  GGATCAAACTACACATGCGTTTTCATTCCAAAAGTGGGTTCTAAATGCCTGGCTGCATCT  9780
9781  GTATGAAATCAAGGCACACTCCAGGAAGACTGCCACGTCGCGCCAACACGTCATACTCAA  9840
9841  TRCCTCAGACTTTCATATTTCTGTGTTGCTGAGATGCCTTTCAATGCAATCGTCTGGGCT  9900
9901  CGTGGATATGTCCCTCAGGTGCGGTGACAGAATGGTGGCACCACGATATGTGTTCTCTTG  9960
9961  TGTTGTTTTTCCTTTTTAAACCCCCATGAACACGAATACTCTGAAAAAAATAAAAAGCTT 10020
10021 TCTGGAAGAAGACACCTTTCTGATAGAGGCTCACACCTACAAATGCTTCACTCTGTCCTT 10080
10081 CCGAGACCTGACAAGCTTTGAGGACCTCACAGCTCCCCTGTGTGTTCATCTCTAGGGATG 10140
10141 TTTGCAATTTCCCAGTCAGCTGTTCTGTCGCAGAATGTTTAATGCACAATTTTTTGCACT 10200
10201 AGTGTGTTATGAATGACTAAGATTCTGATAAAAAAAATAAATTATTTACACAGGGTTTAT 10260
10261 ACACACTATCCATTGTATATAAGCATTATTTCATATTATCAAGCTAAACATTCCCCCATC 10320
10321 AGCTTAGTTGGAGTGTTAGGGAAAAGTATTCCTAGATATGGCACAGATTTTAAAAGGAAA 10380
10381 TACAGTATTGACGAGATTTATTTTATTATTGCTTCAATTAGCTCCATTTACGTGTTGAAT 10440
10441 TCATTGAAGAGGTCCAATGAGAAAAAAACAGAAGCCTCCTTATTTCACACGTTTTCCTCC 10500
10501 TTTAGTACCATCCTCATCCAATTACTGTCTCTCTGATACTACTTAATAGCAGGGGGTTTG 10560
10561 CAGAAATTTCTGTTTGCCATGTAAAACTGTGAATAGTAATTTATTTTAGATAGTCGATGA 10620
10621 ACTTGTGGGTTTTAGCTCACAATGCAGCCTTCCCTTTTGCAGTGTTTTTTTTT   10673
```

Figure 2A

Map of Second Human C3b/C4b Complement Receptor like cDNA (SEQ ID NO:6) and Amino Acid Sequences (SEQ ID NO:7)

```
   1  ACCCTGACGGTTGGTGATGCTGGGAAGGTGGAGACACCAGATCGGTCTTGTACGTGCTC    60
   1  T  L  T  V  G  D  A  G  K  V  G  D  T  R  S  V  L  Y  V  L     20

  61  ACGGGATCCAGTGTTCCTGACCTCATTGTGAGCATGAGCAACCAGATGTGGCTACATCTG   120
  21  T  G  S  S  V  P  D  L  I  V  S  M  S  N  Q  M  W  L  H  L     40

 121  CAGTCGGATGATAGCATTGGCTCACCTGGGTTTAAAGCTGTTTACCAAGAAATTGAAAAG   180
  41  Q  S  D  D  S  I  G  S  P  G  F  K  A  V  Y  Q  E  I  E  K     60

 181  GGAGGGTGTGGGGATCCTGGAATCCCCGCCTATGGAAGCGGACGGGCAGCAGTTTCCTC   240
  61  G  G  C  G  D  P  G  I  P  A  Y  G  K  R  T  G  S  S  F  L     80

 241  CATGGAGATACACTCACCTTTGAATGCCCGGCGGCCTTTGAGCTGGTGGGGGAGAGAGTT   300
  81  H  G  D  T  L  T  F  E  C  P  A  A  F  E  L  V  G  E  R  V    100

 301  ATCACCTGTCAGCAGAACAATCAGTGGTCTGGCAACAAGCCCAGCTGTGTATTTTCATGT   360
 101  I  T  C  Q  Q  N  N  Q  W  S  G  N  K  P  S  C  V  F  S  C    120

 361  TTCTTCAACTTTACGGCATCATCTGGGATTATTCTGTCACCAAATTATCCAGAGGAATAT   420
 121  F  F  N  F  T  A  S  S  G  I  I  L  S  P  N  Y  P  E  E  Y    140

 421  GGGAACAACATGAACTGTGTCTGGTTGATTATCTCGGAGCCAGGAAGTCGAATTCACCTA   480
 141  G  N  N  M  N  C  V  W  L  I  I  S  E  P  G  S  R  I  H  L    160

 481  ATCTTTAATGATTTTGATGTTGAGCCTCAATTTGACTTTCTCGCGGTCAAGGATGATGGC   540
 161  I  F  N  D  F  D  V  E  P  Q  F  D  F  L  A  V  K  D  D  G    180

 541  ATTTCTGACATAACTGTCCTGGGTACTTTTTCTGGCAATGAAGTGCCTTCCCAGCTGGCC   600
 181  I  S  D  I  T  V  L  G  T  F  S  G  N  E  V  P  S  Q  L  A    200

 601  AGCAGTGGGCATATAGTTCGCTTGGAATTTCAGTCTGACCATTCCACTACTGGCAGAGGG   660
 201  S  S  G  H  I  V  R  L  E  F  Q  S  D  H  S  T  T  G  R  G    220

 661  TTCAACATCACTTACACCACATTTGGTCAGAATGAGTGCCATGATCCTGGCATTCCTATA   720
 221  F  N  I  T  Y  T  T  F  G  Q  N  E  C  H  D  P  G  I  P  I    240

 721  AACGGACGACGTTTTGGTGACAGGTTTCTACTCGGGAGCTCGGTTTCTTTCCACTGTGAT   780
 241  N  G  R  R  F  G  D  R  F  L  L  G  S  S  V  S  F  H  C  D    260

 781  GATGGCTTTGTCAAGACCCAGGGATCCGAGTCCATTACCTGCATACTGCAAGACGGGAAC   840
 261  D  G  F  V  K  T  Q  G  S  E  S  I  T  C  I  L  Q  D  G  N    280

 841  GTGGTCTGGAGCTCCACCGTGCCCCGCTGTGAAGCTCCATGTGGTGGACATCTGACAGCG   900
 281  V  V  W  S  S  T  V  P  R  C  E  A  P  C  G  G  H  L  T  A    300

 901  TCCAGCGGAGTCATTTTGCCTCCTGGATGGCCAGGATATTATAAGGATTCTTTACATTGT   960
 301  S  S  G  V  I  L  P  P  G  W  P  G  Y  Y  K  D  S  L  H  C    320

 961  GAATGGATAATTGAAGCAAAACCAGGCCACTCTATCAAAATAACTTTTGACAGATTTCAG  1020
 321  E  W  I  I  E  A  K  P  G  H  S  I  K  I  T  F  D  R  F  Q    340

1021  ACAGAGGTCAATTATGACACCTTGGAGGTCAGAGATGGGCCAGCCAGTTCGTCCCCACTG  1080
 341  T  E  V  N  Y  D  T  L  E  V  R  D  G  P  A  S  S  S  P  L    360
```

Figure 2B

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1081  ATCGGCGAGTACCACGGCACCCAGGCACCCCAGTTCCTCATCAGCACCGGGAACTTCATG  1140
 361  I  G  E  Y  H  G  T  Q  A  P  Q  F  L  I  S  T  G  N  F  M    380

1141  TACCTGCTATTCACCACTGACAACAGCCGCTCCAGCATCGGCTTCCTCATCCACTATGAG  1200
 381  Y  L  L  F  T  T  D  N  S  R  S  S  I  G  F  L  I  H  Y  E    400

1201  AGTGTGACGCTTGAGTCGGATTCCTGCCTGGACCCGGGCATCCCTGTGAACGRCCATCGC  1260
 401  S  V  T  L  E  S  D  S  C  L  D  P  G  I  P  V  N  X  H  R    420

1261  CACGGTGGAGACTTTGGCATCAGGTCCACAGTGACTTTCAGCTGTGACCCGGGGTACACA  1320
 421  H  G  G  D  F  G  I  R  S  T  V  T  F  S  C  D  P  G  Y  T    440

1321  CTAAGTGACGACGAGCCCCTCGTCTGTGAGAGGAACCACCAGTGGAACCACGCCTTGCCC  1380
 441  L  S  D  D  E  P  L  V  C  E  R  N  H  Q  W  N  H  A  L  P    460

1381  AGCTGCGACGCTCTATGTGGAGGCTACATCCAAGGGAAGAGTGGAACAGTCCTTTCTCCT  1440
 461  S  C  D  A  L  C  G  G  Y  I  Q  G  K  S  G  T  V  L  S  P    480

1441  GGGTTTCCAGATTTTTATCCAAACTCTCTAAACYGCACGTGGACCATTGAAGTGTCTCAT  1500
 481  G  F  P  D  F  Y  P  N  S  L  N  X  T  W  T  I  E  V  S  H    500

1501  GGGAAAGGAGTTCAAATGATCTTTCACACCTTTCATCTTGAGAGTTCCCACGACTATTTA  1560
 501  G  K  G  V  Q  M  I  F  H  T  F  H  L  E  S  S  H  D  Y  L    520

1561  CTGATCACAGAGGATGGAAGTTTTTCCGAGCCCGTTGCCAGGCTCACCGGGTCGGTGTTG  1620
 521  L  I  T  E  D  G  S  F  S  E  P  V  A  R  L  T  G  S  V  L    540

1621  CCTCATACGATCAAGGCAGGCCTGTTTGGAAACTTCACTGCCCAGCTTCGGTTTATATCA  1680
 541  P  H  T  I  K  A  G  L  F  G  N  F  T  A  Q  L  R  F  I  S    560

1681  GACTTCTCAATTTCGTACGAGGGCTTCAATATCACATTTTCAGAATATGACCTGGAGCCA  1740
 561  D  F  S  I  S  Y  E  G  F  N  I  T  F  S  E  Y  D  L  E  P    580

1741  TGTGATGATCCTGGAGTCCCTGCCTTCAGCCGAAGAATTGGTTTTCACTTTGGTGTGGGA  1800
 581  C  D  D  P  G  V  P  A  F  S  R  R  I  G  F  H  F  G  V  G    600

1801  GACTCTCTGACGTTTTCCTGCTTCCTGGGATATCGTTTAGAAGGTGCCRCCAAGCTTACC  1860
 601  D  S  L  T  F  S  C  F  L  G  Y  R  L  E  G  A  X  K  L  T    620

1861  TGCCTGGGTGGGGGCCGCCGTGTGTGGAGTGCACCTCTGCCAAGGTGTGTGGCCGAATGT  1920
 621  C  L  G  G  G  R  R  V  W  S  A  P  L  P  R  C  V  A  E  C    640

1921  GGAGCAAGTGTCAAAGGAAATGAAGGAACATTACTGTCTCCAAATTTTCCATCCAATTAT  1980
 641  G  A  S  V  K  G  N  E  G  T  L  L  S  P  N  F  P  S  N  Y    660

1981  GATAATAACCATGAGTGTATCTATAAAATAGAAACAGAAGCCGGCAAGGGCATCCACCTT  2040
 661  D  N  N  H  E  C  I  Y  K  I  E  T  E  A  G  K  G  I  H  L    680

2041  AGAACACGAAGCTTCCAGCTGTTTGAAGGAGATACTCTAAAGGTATATGATGGAAAAGAC  2100
 681  R  T  R  S  F  Q  L  F  E  G  D  T  L  K  V  Y  D  G  K  D    700

2101  AGTTCCTCACGTCCACTGGGCACGTTCACTAAAAATGAACTTCTGGGGCTGATCCTAAAC  2160
 701  S  S  S  R  P  L  G  T  F  T  K  N  E  L  L  G  L  I  L  N    720

2161  AGCACATCCAATCACCTRTGGCTAGAGTTCAACACCAATGGATCTGACACCGACCAAGGT  2220
 721  S  T  S  N  H  L  W  L  E  F  N  T  N  G  S  D  T  D  Q  G    740
```

Figure 2C

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2221  TTTCAACTCACCTATACCAGTTTTGATCTGGTAAAATGTGAGGATCCGGGCATCCCTAAC  2280
 741  F  Q  L  T  Y  T  S  F  D  L  V  K  C  E  D  P  G  I  P  N    760

2281  TACGGCTATAGGATCCGTGATGAAGGCCACTTTACCGACACTGTAGTTCTGTACAGTTGC  2340
 761  Y  G  Y  R  I  R  D  E  G  H  F  T  D  T  V  V  L  Y  S  C    780

2341  AACCCGGGGTACGCCATGCATGGCAGCAACACCCTGACCTGTTTGAGTGGAGACAGGAGA  2400
 781  N  P  G  Y  A  M  H  G  S  N  T  L  T  C  L  S  G  D  R  R    800

2401  GTGTGGGACAAACCACTACCTTCGTGCATAGCGGAATGTGGTGGTCAGATCCATGCAGCC  2460
 801  V  W  D  K  P  L  P  S  C  I  A  E  C  G  G  Q  I  H  A  A    820

2461  ACATCAGGACGAATATTGTCCCCTGGCTATCCAGCTCCGTATGACAACAACCTCCACTGC  2520
 821  T  S  G  R  I  L  S  P  G  Y  P  A  P  Y  D  N  N  L  H  C    840

2521  ACCTGGATTATAGAGGCAGACCCAGGAAAGACCATTAGCCTCCATTTCATTGTTTTCGAC  2580
 841  T  W  I  I  E  A  D  P  G  K  T  I  S  L  H  F  I  V  F  D    860

2581  ACGGAGATGGCTCACGACATCCTCAAGGTCTGGGACGGGCCGGTGGACAGTGACATCCTG  2640
 861  T  E  M  A  H  D  I  L  K  V  W  D  G  P  V  D  S  D  I  L    880

2641  CTGAAGGAGTGGAGTGGCTCCGCCCTTCCGGAGGACATCCACAGCACCTTCAACTCACTC  2700
 881  L  K  E  W  S  G  S  A  L  P  E  D  I  H  S  T  F  N  S  L    900

2701  ACCCTGCAGTTCGACAGCGACTTCTTCATCAGCAAGTCTGGCTTCTCCATCCAGTTCTCC  2760
 901  T  L  Q  F  D  S  D  F  F  I  S  K  S  G  F  S  I  Q  F  S    920

2761  ACCTCAATTGCAGCCACCTGTAACGATCCAGGTATGCCCCAAAATGGCACCCGCTATGGA  2820
 921  T  S  I  A  A  T  C  N  D  P  G  M  P  Q  N  G  T  R  Y  G    940

2821  GACAGCAGAGAGGCTGGAGACACCGTCACATTCCAGTGTGACCCTGGCTATCAGCTCCAA  2880
 941  D  S  R  E  A  G  D  T  V  T  F  Q  C  D  P  G  Y  Q  L  Q    960

2881  GGACAAGCCAAAATCACCTGTGTGCAGCTGAATAACCGGTTCTTTTGGCAACCAGACCCT  2940
 961  G  Q  A  K  I  T  C  V  Q  L  N  N  R  F  F  W  Q  P  D  P    980

2941  CCTACATGCATAGCTGCTTGTGGAGGGAATCTGACGGGCCCAGCAGGTGTTATTTTGTCA  3000
 981  P  T  C  I  A  A  C  G  G  N  L  T  G  P  A  G  V  I  L  S   1000

3001  CCCAACTACCCACAGCCGTATCCTCCTGGGAAGGAATGTGACTGGAGAGTAAAAGTGAAC  3060
1001  P  N  Y  P  Q  P  Y  P  P  G  K  E  C  D  W  R  V  K  V  N   1020

3061  CCGGACTTTGTCATCGCCTTGATATTCAAAAGTTTCAACATGGAGCCCAGCTATGACTTC  3120
1021  P  D  F  V  I  A  L  I  F  K  S  F  N  M  E  P  S  Y  D  F   1040

3121  CTACACATCTATGAAGGGGAAGATTCCAACAGCCCCCTCATTGGGAGTTACCAGGGCTCT  3180
1041  L  H  I  Y  E  G  E  D  S  N  S  P  L  I  G  S  Y  Q  G  S   1060

3181  CAGGCCCCAGAAAGAATAGAGAGTAGCGGAAACAGCCTGTTTCTGGCATTTCGGAGTGAT  3240
1061  Q  A  P  E  R  I  E  S  S  G  N  S  L  F  L  A  F  R  S  D   1080

3241  GCCTCCGTGGGCCTTTCAGGGTTCGCCATTGAATTTAAAGAGAAACCACGGGAAGCTTGT  3300
1081  A  S  V  G  L  S  G  F  A  I  E  F  K  E  K  P  R  E  A  C   1100

3301  TTTGACCCAGGAAATATAATGAATGGGACAAGAGTTGGAACAGACTTCAAGCTTGGCTCC  3360
1101  F  D  P  G  N  I  M  N  G  T  R  V  G  T  D  F  K  L  G  S   1120

3361  ACCATCACCTACCAGTGTGACTCTGGCTATAAGATTCTTGACCCCTCATCCATCACCTGT  3420
1121  T  I  T  Y  Q  C  D  S  G  Y  K  I  L  D  P  S  S  I  T  C   1140
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Figure 2D

```
3421  GTGATTGGGGCTGATGGGAAACCCTCCTGGGACCAAGTGCTGCCCTCCTGCAATGCTCCC  3480
1141  V   I   G   A   D   G   K   P   S   W   D   Q   V   L   P   S   C   N   A   P    1160

3481  TGTGGAGGCCAGTACACGGGATCAGAAGGGGTAGTTTTATCACCAAACTACCCCCATAAT  3540
1161  C   G   G   Q   Y   T   G   S   E   G   V   V   L   S   P   N   Y   P   H   N    1180

3541  TACACAGCTGGTCAAATATGCCTCTATTCCATCACGGTACCAAAGGAATTCGTGGTCTTT  3600
1181  Y   T   A   G   Q   I   C   L   Y   S   I   T   V   P   K   E   F   V   V   F    1200

3601  GGACAGTTTGCCTATTTCCAGACAGCCCTGAATGATTTGGCAGAATTATTTGATGGAACC  3660
1201  G   Q   F   A   Y   F   Q   T   A   L   N   D   L   A   E   L   F   D   G   T    1220

3661  CATGCACAGGCCAGACTTCTCAGCTCACTCTCGGGGTCTCACTCAGGGGAAACATTGCCC  3720
1221  H   A   Q   A   R   L   L   S   S   L   S   G   S   H   S   G   E   T   L   P    1240

3721  TTGGCTACGTCAAATCAAATTCTGCTCCGATTCAGTGCAAAGAGCGGTGCCTCTGCCCGC  3780
1241  L   A   T   S   N   Q   I   L   L   R   F   S   A   K   S   G   A   S   A   R    1260

3781  GGCTTCCACTTCGTGTATCAAGCTGTTCCTCGTACCAGTGACACCCAATGCAGCTCTGTC  3840
1261  G   F   H   F   V   Y   Q   A   V   P   R   T   S   D   T   Q   C   S   S   V    1280

3841  CCCGAGCCCAGATACGGAAGGAGAATTGGTTCTGAGTTTTCTGCCGGCTCCATCGTCCGA  3900
1281  P   E   P   R   Y   G   R   R   I   G   S   E   F   S   A   G   S   I   V   R    1300

3901  TTCGAGTRCAACCCGGGATACCTGCTTCAGGGTTCCACGGCGCTCCACTGCCAGTCCGTG  3960
1301  F   E   X   N   P   G   Y   L   L   Q   G   S   T   A   L   H   C   Q   S   V    1320

3961  CCCAACGCCTTGGCACAGTGGAACGACACGATCCCCAGCTGTGTGGTACCCTGCAGTGGC  4020
1321  P   N   A   L   A   Q   W   N   D   T   I   P   S   C   V   V   P   C   S   G    1340

4021  AATTTCACTCAACGAAGAGGTACAATCCTGTCCCCCGGCTACCCTGAGCCATACGGAAAC  4080
1341  N   F   T   Q   R   R   G   T   I   L   S   P   G   Y   P   E   P   Y   G   N    1360

4081  AACTTGAACTGTATATGGAAGATCATAGTTACGGAGGGCTCGGGAATTCAGATCCAAGTG  4140
1361  N   L   N   C   I   W   K   I   I   V   T   E   G   S   G   I   Q   I   Q   V    1380

4141  ATCAGTTTTGCCACGGAGCAGAACTGGGACTCCCTTGAGATCCACGATGGTGGGGATGTG  4200
1381  I   S   F   A   T   E   Q   N   W   D   S   L   E   I   H   D   G   G   D   V    1400

4201  ACCGCACCCAGACTGGGAAGCTTCTCAGGCACCACAGTACCGGCACTGCTGAACAGTACT  4260
1401  T   A   P   R   L   G   S   F   S   G   T   T   V   P   A   L   L   N   S   T    1420

4261  TCCAACCAACTCTACCTGCATTTCCAGTCTGACATTAGTGTGGCAGCTGCTGGTTTCCAC  4320
1421  S   N   Q   L   Y   L   H   F   Q   S   D   I   S   V   A   A   A   G   F   H    1440

4321  CTGGAATACAAAACTGTAGGTCTTGCTGCATGCCAAGAACCAGCCCTCCCCAGCAACAGC  4380
1441  L   E   Y   K   T   V   G   L   A   A   C   Q   E   P   A   L   P   S   N   S    1460

4381  ATCAAAATCGGAGATCGGTACATGGTGAACGACGTGCTCTCCTTCCAGTGCGAGCCCGGG  4440
1461  I   K   I   G   D   R   Y   M   V   N   D   V   L   S   F   Q   C   E   P   G    1480

4441  TACACCCTGCAGGGCCGTTCCCACATTTCCTGTATGCCAGGGACCGTTCGCCGTTGGAAC  4500
1481  Y   T   L   Q   G   R   S   H   I   S   C   M   P   G   T   V   R   R   W   N    1500

4501  TATCCGTCTCCCCTGTGCATTGCAACCTGTGGAGGGACGCTGAGCACCTTGGGTGGTGTG  4560
1501  Y   P   S   P   L   C   I   A   T   C   G   G   T   L   S   T   L   G   G   V    1520
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Figure 2E

4561 ATCCTGAGCCCCGGCTTCCCAGGTTCTTACCCCAACAACTTAGACTGCACCTGGAGGATC 4620
1521 I L S P G F P G S Y P N N L D C T W R I 1540

4621 TCATTACCCATCGGCTATGGTGCACATATTCAGTTTCTGAATTTTTCTACCGAAGCTAAT 4680
1541 S L P I G Y G A H I Q F L N F S T E A N 1560

4681 CATGACTTCCTTGAAATTCAAAATGGACCTTACCACACCAGCCCCATGATTGGACAATTT 4740
1561 H D F L E I Q N G P Y H T S P M I G Q F 1580

4741 AGCGGCACGGATCTCCCCGCGGCCCTGCTGAGCACAACGCATGAAACCCTCATCCACTTT 4800
1581 S G T D L P A A L L S T T H E T L I H F 1600

4801 TATAGTGACCATTCGCAAAACCGGCAAGGATTTAAACTTGCTTACCAAGCCTATGAATTA 4860
1601 Y S D H S Q N R Q G F K L A Y Q A Y E L 1620

4861 CAGAACTGTCCAGATCCACCCCCATTTCAGAATGGGTACATGATCAACTCGGATTACAGC 4920
1621 Q N C P D P P P F Q N G Y M I N S D Y S 1640

4921 GTGGGGCAATCAGTATCTTTCGAGTGTTATCCTGGGTACATTCTAATAGGCCATCCTGTC 4980
1641 V G Q S V S F E C Y P G Y I L I G H P V 1660

4981 CTCACTTGTCAGCATGGGATCAACAGAAACTGGAACTACCCTTTTCCAAGATGTGATGCC 5040
1661 L T C Q H G I N R N W N Y P F P R C D A 1680

5041 CCTTGTGGGTACAACGTAACTTCTCAGAACGGCACCATCTACTCCCCTGGCTTTCCTGAT 5100
1681 P C G Y N V T S Q N G T I Y S P G F P D 1700

5101 GAGTATCCGATCCTGAAGGACTGCATTTGGCTCATCACGGTGCCTCCAGGGCACGGAGTT 5160
1701 E Y P I L K D C I W L I T V P P G H G V 1720

5161 TACATCAACTTCACCCTGTTACAGACGGAAGCTGTCAACGATTACATTGCTGTTTGGGAC 5220
1721 Y I N F T L L Q T E A V N D Y I A V W D 1740

5221 GGTCCCGATCAGAACTCACCCCAGCTGGGAGTTTTCAGTGGCAACACAGCCCTCGAAACG 5280
1741 G P D Q N S P Q L G V F S G N T A L E T 1760

5281 GCGTATAGCTCCACCAACCAAGTCCTGCTCAAGTTCCACAGCGACTTTTCAAATGGAGGC 5340
1761 A Y S S T N Q V L L K F H S D F S N G G 1780

5341 TTCTTTGTCCTCAATTTCCACGCATTTCAGCTCAAGAAATGTCAACCTCCCCCAGCGGTT 5400
1781 F F V L N F H A F Q L K K C Q P P P A V 1800

5401 CCACAGGCAGAAATGCTTACTGAGGATGATGATTTCGAGATAGGAGATTTTGTGAAGTAC 5460
1801 P Q A E M L T E D D D F E I G D F V K Y 1820

5461 CAGTGCCACCCCGGGTACACCTTGGTGGGGACCGACATTCTGACTTGCAAGCTCAGTTCC 5520
1821 Q C H P G Y T L V G T D I L T C K L S S 1840

5521 CAGTTGCAGTTTGAGGGTTCTCTCCCAACATGTGAAGCACAATGCCCAGCAAATGAAGTC 5580
1841 Q L Q F E G S L P T C E A Q C P A N E V 1860

5581 CGGACTGGATCATCGGGAGTCATTCTCAGTCCAGGGTATCCGGGTAATTATTTTAACTCC 5640
1861 R T G S S G V I L S P G Y P G N Y F N S 1880

5641 CAGACTTGCTCTTGGAGTATTAAAGTGGAACCAAACTACAACATTACCATCTTTGTGGAC 5700
1881 Q T C S W S I K V E P N Y N I T I F V D 1900

Figure 2F

5701 ACATTTCAAAGTGAAAAGCAGTTTGATGCACTGGAAGTGTTTGATGGTTCTTCTGGGCAA 5760
1901 T F Q S E K Q F D A L E V F D G S S G Q 1920

5761 AGTCCTCTGCTAGTAGTCTTAAGTGGGAATCATACTGAACAATCAAATTTTACAAGCAGG 5820
1921 S P L L V V L S G N H T E Q S N F T S R 1940

5821 AGTAATCAGTTATATCTCCGCTGGTCCACTGACCATGCCACCAGTAAGAAAGGATTCAAG 5880
1941 S N Q L Y L R W S T D H A T S K K G F K 1960

5881 ATTCGCTATGCAGCACCTTACTGCAGTTTGACCCACCCCCTGAAGAATGGGGGTATTCTA 5940
1961 I R Y A A P Y C S L T H P L K N G G I L 1980

5941 AACAGGACTGCAGGAGCGGTTGGAAGCAAAGTGCATTATTTTTGCAAGCCTGGATACCGA 6000
1981 N R T A G A V G S K V H Y F C K P G Y R 2000

6001 ATGGTCGGCCACAGCAATGCAACCTGTAGACGAAACCCACTTGGCATGTACCAGTGGGAC 6060
2001 M V G H S N A T C R R N P L G M Y Q W D 2020

6061 TCCCTCACGCCACTCTGCCAGGCTGTGTCCTGTGGAATCCCAGAATCCCCAGGAAACGGT 6120
2021 S L T P L C Q A V S C G I P E S P G N G 2040

6121 TCATTTACCGGGAACGAGTTCACTTTGGACAGTAAAGTGGTCTATGAATGTCATGAGGGC 6180
2041 S F T G N E F T L D S K V V Y E C H E G 2060

6181 TTCAAGCTTGAATCCAGCCAGCAAGCAACAGCCGTGTGTCAAGAAGATGGGCTGTGGAGT 6240
2061 F K L E S S Q Q A T A V C Q E D G L W S 2080

6241 AACAAGGGGAAGCCGCCCACGTGTAAGCCGGTCGCTTGCCCCAGCATTGAAGCTCAGCTC 6300
2081 N K G K P P T C K P V A C P S I E A Q L 2100

6301 TCAGAACATGTCATCTGGAGGCTGGTTTCAGGATCCTTGAATGAGTACGGTGCTCAAGTA 6360
2101 S E H V I W R L V S G S L N E Y G A Q V 2120

6361 TTGCTGAGCTGCAGTCCTGGTTACTACTTAGAAGGCTGGAGGCTCCTGCGGTGCCAGGCC 6420
2121 L L S C S P G Y Y L E G W R L L R C Q A 2140

6421 AATGGGACGTGGAACATAGGAGATGAGAGGCCAAGCTGTCGAGTTATCTCGTGTGGAAGC 6480
2141 N G T W N I G D E R P S C R V I S C G S 2160

6481 CTTTCCTTTCCCCCAAATGGCAACAAGATTGGAACGTTGACAGTTTATGGGGCCACAGCT 6540
2161 L S F P P N G N K I G T L T V Y G A T A 2180

6541 ATATTTACGTGCAACACCGGCTACACGCTTGTGGGGTCTCATGTCAGAGAGTGCTTGGCA 6600
2181 I F T C N T G Y T L V G S H V R E C L A 2200

6601 AATGGGCTCTGGAGCGGCAGCGAAACTCGATGTCTGGCTGGCCACTGCGGTTCCCCAGAC 6660
2201 N G L W S G S E T R C L A G H C G S P D 2220

6661 CCGATTGTGAACGGTCACATTAGTGGAGATGGCTTCAGTTACAGAGACACGGTGGTTTAC 6720
2221 P I V N G H I S G D G F S Y R D T V V Y 2240

6721 CAGTGCAATCCTGGTTTCCGGCTTGTGGGAACTTCCGTGAGGATATGCCTGCAAGACCAC 6780
2241 Q C N P G F R L V G T S V R I C L Q D H 2260

6781 AAGTGGTCTGGACAAACGCCTGTCTGTGTCCCCATCACATGTGGTCACCCTGGAAACCCT 6840
2261 K W S G Q T P V C V P I T C G H P G N P 2280

Figure 2G

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6841 GCCCACGGATTCACTAATGGCAGTGAGTTCAACCTGAATGATGTCGTGAATTTCACCTGC 6900
2281 A  H  G  F  T  N  G  S  E  F  N  L  N  D  V  V  N  F  T  C   2300

6901 AACACGGGCTATTTGCTGCAGGGCGTGTCTCGAGCCCAGTGTCGGAGCAACGGCCAGTGG 6960
2301 N  T  G  Y  L  L  Q  G  V  S  R  A  Q  C  R  S  N  G  Q  W   2320

6961 AGTAGCCCTCTGCCCACGTGTCGAGTGGTGAACTGTTCTGATCCAGGCTTTGTGGAAAAT 7020
2321 S  S  P  L  P  T  C  R  V  V  N  C  S  D  P  G  F  V  E  N   2340

7021 GCCATTCGTCACGGGCAACAGAACTTCCCTGAGAGTTTTGAGTATGGAATGAGTATCCTG 7080
2341 A  I  R  H  G  Q  Q  N  F  P  E  S  F  E  Y  G  M  S  I  L   2360

7081 TACCATTGCAAGAAGGGATTTTACTTGCTGGGATCTTCAGCCTTGACCTGTATGGCAAAT 7140
2361 Y  H  C  K  K  G  F  Y  L  L  G  S  S  A  L  T  C  M  A  N   2380

7141 GGCTTATGGGACCGATCCCTGCCCAAGTGTTTGGCTATATCGTGTGGACACCCAGGGGTC 7200
2381 G  L  W  D  R  S  L  P  K  C  L  A  I  S  C  G  H  P  G  V   2400

7201 CCTGCCAACGCCGTCCTCACTGGAGAGCTGTTTACCTATGGCGCCGTCGTGCACTACTCC 7260
2401 P  A  N  A  V  L  T  G  E  L  F  T  Y  G  A  V  V  H  Y  S   2420

7261 TGCAGAGGGAGCGAGAGCCTCATAGGCAACGACACGAGAGTGTGCCAGGAAGACAGTCAC 7320
2421 C  R  G  S  E  S  L  I  G  N  D  T  R  V  C  Q  E  D  S  H   2440

7321 TGGAGCGGGGCACTGCCCCACTGCACAGGAAATAATCCTGGATTCTGTGGTGATCCGGGG 7380
2441 W  S  G  A  L  P  H  C  T  G  N  N  P  G  F  C  G  D  P  G   2460

7381 ACCCCAGCACATGGGTCTCGGCTTGGTGATGACTTTAAGACAAAGAGTCTTCTCCGCTTC 7440
2461 T  P  A  H  G  S  R  L  G  D  D  F  K  T  K  S  L  L  R  F   2480

7441 TCCTGTGAAATGGGGCACCAGCTGAGGGGCTCCCCTGAACGCACGTGTTTGCTCAATGGG 7500
2481 S  C  E  M  G  H  Q  L  R  G  S  P  E  R  T  C  L  L  N  G   2500

7501 TCATGGTCAGGACTGCAGCCGGTGTGTGAGGCCGTGTCCTGTGGCAACCCTGGCACACCC 7560
2501 S  W  S  G  L  Q  P  V  C  E  A  V  S  C  G  N  P  G  T  P   2520

7561 ACCAACGGAATGATTGTCAGTAGTGATGGCATTCTGTTCTCCAGCTCGGTCATCTATGCC 7620
2521 T  N  G  M  I  V  S  S  D  G  I  L  F  S  S  S  V  I  Y  A   2540

7621 TGCTGGGAAGGCTACAAGACCTCAGGGCTCATGACACGGCATTGCACAGCCAATGGGACC 7680
2541 C  W  E  G  Y  K  T  S  G  L  M  T  R  H  C  T  A  N  G  T   2560

7681 TGGACAGGCACTGCTCCCGACTGCACAATTATAAGTTGTGGGGATCCAGGCACACTAGCA 7740
2561 W  T  G  T  A  P  D  C  T  I  I  S  C  G  D  P  G  T  L  A   2580

7741 AATGGCATCCAGTTTGGGACCGACTTCACCTTCAACAAGACTGTGAGCTATCAGTGTAAC 7800
2581 N  G  I  Q  F  G  T  D  F  T  F  N  K  T  V  S  Y  Q  C  N   2600

7801 CCAGGCTATGTCATGGAAGCAGTCACATCCGCCACTATTCGCTGTACCAAAGACGGCAGG 7860
2601 P  G  Y  V  M  E  A  V  T  S  A  T  I  R  C  T  K  D  G  R   2620

7861 TGGAATCCGAGCAAACCTGTCTGCAAAGCCGTGCTGTGTCCTCAGCCGCCGCCGGTGCAG 7920
2621 W  N  P  S  K  P  V  C  K  A  V  L  C  P  Q  P  P  P  V  Q   2640

7921 AATGGAACAGTGGAGGGAAGTGATTTCCGCTGGGGCTCCAGCATAAGTTACAGCTGCATG 7980
2641 N  G  T  V  E  G  S  D  F  R  W  G  S  S  I  S  Y  S  C  M   2660
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Figure 2H

7981 GACGGTTACCAGCTCTCTCACTCCGCCATCCTCTCCTGTGAAGGTCGCGGGGTGTGGAAA 8040
2661 D G Y Q L S H S A I L S C E G R G V W K 2680

8041 GGAGAGATCCCCCAGTGTCTCCCTGTGTTCTGCGGAGACCCTGGCATCCCCGCAGAAGGG 8100
2681 G E I P Q C L P V F C G D P G I P A E G 2700

8101 CGACTTAGTGGGAAAAGTTTCACCTATAAGTCCGAAGTCTTCTTCCAGTGCAAATCTCCA 8160
2701 R L S G K S F T Y K S E V F F Q C K S P 2720

8161 TTTATACTCGTGGGATCCTCCAGAAGAGTCTGCCAAGCTGACGGCACGTGGAGCGGCATA 8220
2721 F I L V G S S R R V C Q A D G T W S G I 2740

8221 CAACCCACCTGCATTGATCCTGCTCATAACACCTGCCCAGACCCTGGTACGCCACACTTT 8280
2741 Q P T C I D P A H N T C P D P G T P H F 2760

8281 GGAATACAGAATAGCTCCAGAGGCTATGAGGTTGGAAGCACGGTTTTTTTCAGGTGCAGA 8340
2761 G I Q N S S R G Y E V G S T V F F R C R 2780

8341 AAAGGCTACCATATTCAAGGTTCCACGACTCGCACCTGCCTTGCCAATTTAACATGGAGT 8400
2781 K G Y H I Q G S T T R T C L A N L T W S 2800

8401 GGGATACAGACCGAATGTATACCTCATGCCTGCAGACAGCCAGAAACCCCGGCACACGCG 8460
2801 G I Q T E C I P H A C R Q P E T P A H A 2820

8461 GATGTGAGAGCCATCGATCTTCCTACTTTCGGCTACACCTTAGTGTACACCTGCCATCCA 8520
2821 D V R A I D L P T F G Y T L V Y T C H P 2840

8521 GGCTTTTTCCTCGCAGGGGGATCTGAGCACAGAACATGTAAAGCAGACATGAAATGGACA 8580
2841 G F F L A G G S E H R T C K A D M K W T 2860

8581 GGAAAGTCGCCTGTGTGTAAAAGTAAAGGAGTGAGAGAAGTTAATGAAACAGTTACTAAA 8640
2861 G K S P V C K S K G V R E V N E T V T K 2880

8641 ACTCCAGTTCCTTCAGATGTCTTTTTCGTCAATTCACTGTGGAAGGGGTATTATGAATAT 8700
2881 T P V P S D V F F V N S L W K G Y Y E Y 2900

8701 TTAGGGAAAAGACAACCCGCCACTCTAACTGTTGACTGGTTCAATGCAACAAGCAGTAAG 8760
2901 L G K R Q P A T L T V D W F N A T S S K 2920

8761 GTGAATGCCACCTTCAGCGAAGCCTCGCCAGTGGAGCTGAAGTTGACAGGCATTTACAAG 8820
2921 V N A T F S E A S P V E L K L T G I Y K 2940

8821 AAGGAGGAGGCCCACTTACTCCTGAAAGCTTTTCAAATTAAAGGCCAGGCAGATATTTTT 8880
2941 K E E A H L L L K A F Q I K G Q A D I F 2960

8881 GTAAGCAAGTTCGAAAATGACAACTGGGGACTAGATGGTTATGTGTCATCTGGACTTGAA 8940
2961 V S K F E N D N W G L D G Y V S S G L E 2980

8941 AGAGGAGGATTTACTTTTCAAGGTGACATTCATGGAAAAGACTTTGGAAAATTTAAGCTA 9000
2981 R G G F T F Q G D I H G K D F G K F K L 3000

9001 GAAAGGCAAGATCCTTTAAACCCAGATCAAGACTCTTCCAGTCATTACCACGGCACCAGC 9060
3001 E R Q D P L N P D Q D S S S H Y H G T S 3020

9061 AGTGGCTCTGTGGCGGCTGCCATTCTGGTTCCTTTCTTTGCTCTAATTTTATCAGGGTTT 9120
3021 S G S V A A A I L V P F F A L I L S G F 3040

Figure 2I

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 9121  GCATTTTACCTCTACAAACACAGAACGAGACCAAAAGTTCAATACAATGGCTATGCTGGG  9180
 3041  A  F  Y  L  Y  K  H  R  T  R  P  K  V  Q  Y  N  G  Y  A  G   3060

 9181  CATGAAAACAGCAATGGACAAGCATCGTTTGAAAACCCCATGTATGATACAAACTTAAAA  9240
 3061  H  E  N  S  N  G  Q  A  S  F  E  N  P  M  Y  D  T  N  L  K   3080

 9241  CCCACAGAAGCCAAGGCTGTGAGGTTTGACACAACTCTGAACACAGTCTGTACAGTGGTA  9300
 3081  P  T  E  A  K  A  V  R  F  D  T  T  L  N  T  V  C  T  V  V   3100

 9301  TAGCCCTCAGTGCCCCAACAGGACTGATTCATAGCCATACCTCTGATGGACAAGCAGTGA  9360
 3101  *                                                             3101
 9361  TTCCTTTGGTGCCATATACCACTCTCCCYTCCACTCTGGCTTTACTGCAGCGATCTTCAA  9420
 9421  CCTTGTCTACTGGCATAAGTGCAGCGGGGATCTCTACTCAAATGTGTCAGGGTCTTCTAC  9480
 9481  GGATCAAACTACACATGCGTTTTCATTCCAAAAGTGGGTTCTAAATGCCTGGCTGCATCT  9540
 9541  GTATGAAATCAAGGCACACTCCAGGAAGACTGCCACGTCGCGCCAACACGTCATACTCAA  9600
 9601  TRCCTCAGACTTTCATATTTCTGTGTTGCTGAGATGCCTTTCAATGCAATCGTCTGGGCT  9660
 9661  CGTGGATATGTCCCTCAGGTGCGGTGACAGAATGGTGGCACCACGATATGTGTTCTCTTG  9720
 9721  TGTTGTTTTTCCTTTTTAAACCCCCATGAACACGAATACTCTGAAAAAAATAAAAAGCTT  9780
 9781  TCTGGAAGAAGACACCTTTCTGATAGAGGCTCACACCTACAAATGCTTCACTCTGTCCTT  9840
 9841  CCGAGACCTGACAAGCTTTGAGGACCTCACAGCTCCCCTGTGTGTTCATCTCTAGGGATG  9900
 9901  TTTGCAATTTCCCAGTCAGCTGTTCTGTCGCAGAATGTTTAATGCACAATTTTTTGCACT  9960
 9961  AGTGTGTTATGAATGACTAAGATTCTGATAAAAAAAATAAATTATTTACACAGGGTTTAT 10020
10021  ACACACTATCCATTGTATATAAGCATTATTTCATATTATCAAGCTAAACATTCCCCCATC 10080
10081  AGCTTAGTTGGAGTGTTAGGGAAAAGTATTCCTAGATATGGCACAGATTTTAAAAGGAAA 10140
10141  TACAGTATTGACGAGATTTATTTTATTATTGCTTCAATTAGCTCCATTTACGTGTTGAAT 10200
10201  TCATTGAAGAGGTCCAATGAGAAAAAAACAGAAGCCTCCTTATTTCACACGTTTTCCTCC 10260
10261  TTTAGTACCATCCTCATCCAATTACTGTCTCTCTGATACTACTTAATAGCAGGGGGTTTG 10320
10321  CAGAAATTTCTGTTTGCCATGTAAAACTGTGAATAGTAATTTATTTTAGATAGTCGATGA 10380
10381  ACTTGTGGGTTTTAGCTCACAATGCAGCCTTCCCTTTTGCAGTGTTTTTTTTT        10433
```

Figure 2

Map of Rat C3b/C4b Complement Receptor like cDNA (SEQ ID NO:3) and Amino Acid Sequences (SEQ ID NO:4)

```
   1 GATGCCGGGAAGGTGGGGGACACCAGATCCGTCTTGTACGTGCTTACAGGCTCCAGTGTC   60
   1 D  A  G  K  V  G  D  T  R  S  V  L  Y  V  L  T  G  S  S  V     20

  61 CCTGACCTCATCGTGAGCATGAGCAATCAGATGTGGCTCCACCTGCAGTCAGACGACAGC  120
  21 P  D  L  I  V  S  M  S  N  Q  M  W  L  H  L  Q  S  D  D  S    40

 121 ATTGGTTCCCCAGGATTTAAAGCTGTGTACCAAGAAATCGAGAAGGGAGGCTGCGGGGAC  180
  41 I  G  S  P  G  F  K  A  V  Y  Q  E  I  E  K  G  G  C  G  D    60

 181 CCTGGCATCCCAGCCTACGGGAAGCGGACTGGCAGCAGCTTCTTGCACGGGGACACGCTC  240
  61 P  G  I  P  A  Y  G  K  R  T  G  S  S  F  L  H  G  D  T  L    80

 241 ACCTTTGAGTGCCAGGCAGCTTTTGAGCTGGTAGGAGAGAGAGTGATTACGTGCCAGAGA  300
  81 T  F  E  C  Q  A  A  F  E  L  V  G  E  R  V  I  T  C  Q  R   100

 301 AACAACCAGTGGTCCGGCAACAAGCCAAGCTGTGTGTTTTCATGTTTCTTCAACTTCACG  360
 101 N  N  Q  W  S  G  N  K  P  S  C  V  F  S  C  F  F  N  F  T   120

 361 GCGTCCTCTGGGATCATCCTGTCGCCAAACTATCCTGAGGAATATGGCAACAACATGAAT  420
 121 A  S  S  G  I  I  L  S  P  N  Y  P  E  E  Y  G  N  N  M  N   140

 421 TGTGTGTGGTTGATTATATCTGAGCCCGGGAGCCGGATTCACCTCATCTTCAATGATTTC  480
 141 C  V  W  L  I  I  S  E  P  G  S  R  I  H  L  I  F  N  D  F   160

 481 GATGTGGAGCCTCAGTTTGACTTCCTTGCGGTCAAAGATGATGGGATTTCTGACATCACA  540
 161 D  V  E  P  Q  F  D  F  L  A  V  K  D  D  G  I  S  D  I  T   180

 541 GTCCTCGGGACTTTCTCTGGCAATGAGGTGCCTGCACAGCTGGCC.GCAGTGGACACATA  600
 181 V  L  G  T  F  S  G  N  E  V  P  A  Q  L  A  X  S  G  H  I   200

 601 GTACGCCTGGAGTTTCAGTCCGATCACTCTACCACGGGCAGAGGGTTCAACATCATATAC  660
 201 V  R  L  E  F  Q  S  D  H  S  T  T  G  R  G  F  N  I  I  Y   220

 661 ACCACATTTGGTCAGAACGAGTGTCATGACCCTGGGATCCCTGTGAATGGACGGCGCTTT  720
 221 T  T  F  G  Q  N  E  C  H  D  P  G  I  P  V  N  G  R  R  F   240

 721 GGAGACAGGTTTCTGCTGGGAAGTTCTGTGTCCTTCCACTGTGATGATGGCTTTGTGAAG  780
 241 G  D  R  F  L  L  G  S  S  V  S  F  H  C  D  D  G  F  V  K   260

 781 ACTCAGGGTTCTGAGTCTATCACATGCATCTTGCAAGATGGAAACGTGGTCTGGAGCTCT  840
 261 T  Q  G  S  E  S  I  T  C  I  L  Q  D  G  N  V  V  W  S  S   280

 841 ACTGTCCCTCGCTGTGAAGCTCCTTGTGGTGGGCATCTGACAGCTTCTAGTGGGGTCATA  900
 281 T  V  P  R  C  E  A  P  C  G  G  H  L  T  A  S  S  G  V  I   300

 901 TTACCTCCAGGATGGCCAGGATATTACAAAGATTCTTTAAATTGCGAATGGGTCATTGAA  960
 301 L  P  P  G  W  P  G  Y  Y  K  D  S  L  N  C  E  W  V  I  E   320

 961 GCCAAACCAGGACATTCCATCAAAATAACATTTGACAGGTTCCAGACAGAAGTCAATTAT 1020
 321 A  K  P  G  H  S  I  K  I  T  F  D  R  F  Q  T  E  V  N  Y   340

1021 GATACTCTGGAAGTCCGGGATGGGCCAACCAGCTCATCCCCACTGATTGGGGAGTACCAT 1080
 341 D  T  L  E  V  R  D  G  P  T  S  S  S  P  L  I  G  E  Y  H   360
```

Figure 3A

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1081 GGCACCCAGGCTCCACAGTTCCTCATCAGCACAGGGAACTACATGTACCTGCTGTTTACC 1140
361  G  T  Q  A  P  Q  F  L  I  S  T  G  N  Y  M  Y  L  L  F  T  380

1141 ACTGACAGCAGCCGCGCTAGTGTTGGCTTCCTCATCCACTATGAGAGTGTGACTCTTGAA 1200
381  T  D  S  S  R  A  S  V  G  F  L  I  H  Y  E  S  V  T  L  E  400

1201 TCTGACTCCTGTCTGGACCCGGGCATCCCTGTAAATGGTCATCGGCATGGCAGTAACTTT 1260
401  S  D  S  C  L  D  P  G  I  P  V  N  G  H  R  H  G  S  N  F  420

1261 GGTATCAGATCTACAGTGACCTTCAGCTGTGACCCTGGGTACACGCTCAGTGATGACGAT 1320
421  G  I  R  S  T  V  T  F  S  C  D  P  G  Y  T  L  S  D  D  D  440

1321 CCCCTCATCTGTGAGAAGAACCATCAGTGGAACCACGCCTTGCCCAGCTGTGATGCCCTG 1380
441  P  L  I  C  E  K  N  H  Q  W  N  H  A  L  P  S  C  D  A  L  460

1381 TGTGGAGGCTACATCCATGGAAAGAGTGGGACTGTTCTTTCACCAGGATTTCCAGACTTT 1440
461  C  G  G  Y  I  H  G  K  S  G  T  V  L  S  P  G  F  P  D  F  480

1441 TATCCAAACTCTCTGAACTGTACATGGACCATTGAAGTCTCTCATGGCAAGGGAGTGCAG 1500
481  Y  P  N  S  L  N  C  T  W  T  I  E  V  S  H  G  K  G  V  Q  500

1501 ATGAATTTCCACACCTTTCACCTTGAAAGTTCCCACGACTATTTGCTGATCACAGAGGAT 1560
501  M  N  F  H  T  F  H  L  E  S  S  H  D  Y  L  L  I  T  E  D  520

1561 GGGAGTTTCTCAGAGCCGGTAGCCAGGCTCACTGGGTCGGTCCTGCCTCACACCATTAAG 1620
521  G  S  F  S  E  P  V  A  R  L  T  G  S  V  L  P  H  T  I  K  540

1621 GCTGGCTTGTTTGGAAACTTCACTGCGCAACTCAGGTTCATCTCTGACTTCTCCATCTCC 1680
541  A  G  L  F  G  N  F  T  A  Q  L  R  F  I  S  D  F  S  I  S  560

1681 TATGAAGGCTTCAACATTACGTTTGCAGAATATGACCTAgAACCCTGTGATGACCCTGGA 1740
561  Y  E  G  F  N  I  T  F  A  E  Y  D  L  E  P  C  D  D  P  G  580

1741 GTCCCTGCCTACAGTCGCAGAATTGGGTTCCAGTTCGGTGTGGGTGACACCCTGGCTTTC 1800
581  V  P  A  Y  S  R  R  I  G  F  Q  F  G  V  G  D  T  L  A  F  600

1801 ACCTGCTTCCAGGGATACCGCTTAGAAGGTGCAACCAAGCTTACCTGCCTGGGTGGGGGA 1860
601  T  C  F  Q  G  Y  R  L  E  G  A  T  K  L  T  C  L  G  G  G  620

1861 CGCCGAGTGTGGAGTGCACCTCTGCCAAGGTGTGTGGCTGAATGTGGAGCAAGCGTCAAA 1920
621  R  R  V  W  S  A  P  L  P  R  C  V  A  E  C  G  A  S  V  K  640

1921 GGAAATGAAGGAACATTACTCTCTCCAAATTTCCCATCCAATTATGATAATAACCATGAG 1980
641  G  N  E  G  T  L  L  S  P  N  F  P  S  N  Y  D  N  N  H  E  660

1981 TGTATCTATAAAATAGAAACAGAAGCCGGAAAGGGGATCCATCTCAGAGCCCGAACCTTC 2040
661  C  I  Y  K  I  E  T  E  A  G  K  G  I  H  L  R  A  R  T  F  680

2041 CAACTCTTCGAAGGAGACACTCTAAAGGTTTATGATGGAAAGGACAGCTCCTCGAGGTCA 2100
681  Q  L  F  E  G  D  T  L  K  V  Y  D  G  K  D  S  S  S  R  S  700

2101 CTGGGAGTCTTCACAAGAAGTGAACTGATGGGGCTGGTGCTAAACAGCACCTCCAACCAC 2160
701  L  G  V  F  T  R  S  E  L  M  G  L  V  L  N  S  T  S  N  H  720

2161 CTGAGGCTGGAGTTCAACTCTAACGGGTCAGATACCGCCCAAGGCTTCCAGCTCACCTAC 2220
721  L  R  L  E  F  N  S  N  G  S  D  T  A  Q  G  F  Q  L  T  Y  740
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Figure 3C

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2221  ACCAGTTTTGACCTAGTGAAATGTGAGGATCCAGGCATCCCTAACTATGGCTACAGGATC  2280
 741  T   S   F   D   L   V   K   C   E   D   P   G   I   P   N   Y   G   Y   R   I    760

2281  CGAGATGATGGTCACTTCACAGACACTGTGGTTCTCTACAGCTGCAACCCAGGCTACGCA  2340
 761  R   D   D   G   H   F   T   D   T   V   V   L   Y   S   C   N   P   G   Y   A    780

2341  ATGCATGGCAGCAGTACCCtGACCtGCCTGAGTGGGGACCGAAGGGTGTGGGACAAACCT  2400
 781  M   H   G   S   S   T   L   T   C   L   S   G   D   R   R   V   W   D   K   P    800

2401  ATGCCTTCCTGTGTGGCGGAATGTGGTGGTCTCGTCCATGCAGCCACATCAGGACGCATA  2460
 801  M   P   S   C   V   A   E   C   G   G   L   V   H   A   A   T   S   G   R   I    820

2461  CTCTCTCCTGGCTACCCTGCCCCATATGACAACAACCTTCATTGCACTTGGACCATAGAG  2520
 821  L   S   P   G   Y   P   A   P   Y   D   N   N   L   H   C   T   W   T   I   E    840

2521  GCTGATCCTGGCAAGACCAYCAGCCTCCATTTCATTGTGTTTGACACTGAAACGGCGCAC  2580
 841  A   D   P   G   K   T   X   S   L   H   F   I   V   F   D   T   E   T   A   H    860

2581  GACATCCTCAAGGTCTGGGATGGTCCAGTGGACAGCAACATCCTGCTGAAGGAGTGGAGC  2640
 861  D   I   L   K   V   W   D   G   P   V   D   S   N   I   L   L   K   E   W   S    880

2641  GGCTCGGCCCTTCCTGAGGACATCCACAGCACCTTCAACTCGCTCACCCTGCAGTTCGAT  2700
 881  G   S   A   L   P   E   D   I   H   S   T   F   N   S   L   T   L   Q   F   D    900

2701  AGTGACTTCTTCATCAGCAAGTCCGGCTTCTCCATCCAGTTCTCTACTTCCATTGCATCC  2760
 901  S   D   F   F   I   S   K   S   G   F   S   I   Q   F   S   T   S   I   A   S    920

2761  ACCTGCAATGACCCTGGGATGCCTCAGAATGGAACCCGCTATGGTGACAGCCGGGAACCT  2820
 921  T   C   N   D   P   G   M   P   Q   N   G   T   R   Y   G   D   S   R   E   P    940

2821  GGAGACACCATCACCTTCCAGTGTGACCCTGGATACCAGCTCCAAGGGCAAGCCAAGATC  2880
 941  G   D   T   I   T   F   Q   C   D   P   G   Y   Q   L   Q   G   Q   A   K   I    960

2881  ACTTGTGTGCAGCTTAACAACCGCTTCTTCTGGCAACCAGACCCTCCGTCATGCATAGCT  2940
 961  T   C   V   Q   L   N   N   R   F   F   W   Q   P   D   P   P   S   C   I   A    980

2941  GCTTGTGGTGGGAATCTGACAGGCCCTGCTGGAGTGATTTTATCCCCAAACTACCCACAG  3000
 981  A   C   G   G   N   L   T   G   P   A   G   V   I   L   S   P   N   Y   P   Q   1000

3001  CCATACCCTCCTGGGAAGGAGTGTGACTGGAGAATTAAGGTGAACCCAGACTTTGTCATT  3060
1001  P   Y   P   P   G   K   E   C   D   W   R   I   K   V   N   P   D   F   V   I   1020

3061  GCCTTAATATTCAAAAGTTTTAGCATGGAGCCAAGTTACGACTTCCTGCATATCTATGAA  3120
1021  A   L   I   F   K   S   F   S   M   E   P   S   Y   D   F   L   H   I   Y   E   1040

3121  GGGAAGGACTCCAACAGCCCACTGATCGGAAGCTTCCAGGGTTCTCAAGCCCCAGAGAGG  3180
1041  G   K   D   S   N   S   P   L   I   G   S   F   Q   G   S   Q   A   P   E   R   1060

3181  ATTGAGAGCAGTGGTAACAGCCTCTTCCTGGCATTCAGGAGTGATGCCTCTGTTGGCCTG  3240
1061  I   E   S   S   G   N   S   L   F   L   A   F   R   S   D   A   S   V   G   L   1080

3241  TCCGGGTTTGCCATTGAATTTAAAGAGAAACCACGGGAAGCTTGCTTTGACCCTGGGAAC  3300
1081  S   G   F   A   I   E   F   K   E   K   P   R   E   A   C   F   D   P   G   N   1100

3301  ATAATGAACGGGACAAGGATTGGAACGGACTTTAAGCTGGGCTCTACAGTTACCTATCAA  3360
1101  I   M   N   G   T   R   I   G   T   D   F   K   L   G   S   T   V   T   Y   Q   1120
```

Figure 3D

3361 TGTGACTCTGGTTACAAGATTGTGGATCCCTCATCCATTGAGTGTGTGACAGGGGCTGAT 3420
1121 C D S G Y K I V D P S S I E C V T G A D 1140

3421 GGGAAGCCGTCCTGGGACCGGGCACTGCCTGCCTGCCAAGCACCCTGTGGAGGCCAATAC 3480
1141 G K P S W D R A L P A C Q A P C G G Q Y 1160

3481 ATGGGCTCGGAGGGGGTAGTTTTGTCACCAAACTACCCTCATAACTACACGGCTGGGCAG 3540
1161 M G S E G V V L S P N Y P H N Y T A G Q 1180

3541 ATATGCATCTATTCCATCACGGTGCCCAAGGAATTTGTGGTGTTTGGACAGTTTGCCTAT 3600
1181 I C I Y S I T V P K E F V V F G Q F A Y 1200

3601 TTCCAGACTGCGCTGAACGACTTGGCAGAATTGTTTGATGGAACCCATCCTCAGGCCAGG 3660
1201 F Q T A L N D L A E L F D G T H P Q A R 1220

3661 CTTCTCAGTTCTCTCTCTGGTTCCCATTCAGGTGAAACACTCCCGCTGGCTACATCCAAT 3720
1221 L L S S L S G S H S G E T L P L A T S N 1240

3721 CAGATTCTGCTTCGCTTCAGCGCAAAGAGCGGAGCTTCTGCACGGGGTTTCCACTTCGTC 3780
1241 Q I L L R F S A K S G A S A R G F H F V 1260

3781 TACCAAGCCGTCCCACGCACCAGTGACACGCAGTGCAGCTCCGTCCCTGAGCCCAGATAT 3840
1261 Y Q A V P R T S D T Q C S S V P E P R Y 1280

3841 GGGAGAAGGATTGGTTCTGAGTTCTCTGCAGGCTCCATCGTCCGATTCGAGTGCAACCCA 3900
1281 G R R I G S E F S A G S I V R F E C N P 1300

3901 GGTTACCTGCTGCAAGGCTCCACAGCCATCCGTTGTCAGTCTGTGCCAAACGCTTTGGCC 3960
1301 G Y L L Q G S T A I R C Q S V P N A L A 1320

3961 CAGTGGAATGACACCATCCCAAGCTGTGTAGTTCCATGCAGTGGCAATTTCACTCAGAGA 4020
1321 Q W N D T I P S C V V P C S G N F T Q R 1340

4021 AGAGGGACAATCTTATCTCCAGGCTACCCTGAGCCCTATGGGAACAACCTGAACTGTGTA 4080
1341 R G T I L S P G Y P E P Y G N N L N C V 1360

4081 TGGAAGATCATAGTATCGGAGGGCTCAGGGATCCAGATCCAAGTGATTAGCTTTGCCACG 4140
1361 W K I I V S E G S G I Q I Q V I S F A T 1380

4141 GAGCAGAACTGGGACTCCCTGGAGATCCATGACGGAGGAGACATGACGGCCCCCAGACTG 4200
1381 E Q N W D S L E I H D G G D M T A P R L 1400

4201 GGCAGCTTCTCAGGTACCACAGTGCCCGCACTGCTGAATAGCACCTCCAACCAGCTCTGC 4260
1401 G S F S G T T V P A L L N S T S N Q L C 1420

4261 CTGCACTTCCAGTCGGACATCAGTGTTGCCGCTGCGGGCTTTCACCTGGAATACAAAACG 4320
1421 L H F Q S D I S V A A A G F H L E Y K T 1440

4321 GTGGGTCTGGCTGCGTGCCAGGAACCTGCTCTCCCGAGCAACGGCATCAAGATAGGAGAC 4380
1441 V G L A A C Q E P A L P S N G I K I G D 1460

4381 CGCTATATGGTGAACGATGTGCTGTCCTTCCAGTGCGAGCCTGGGTACACCTTGCAGGGC 4440
1461 R Y M V N D V L S F Q C E P G Y T L Q G 1480

4441 CGCTCACACATTTCTTGTATGCCGGGAACTGTACGTCGCTGGAACTATCCTTCCCCTCTG 4500
1481 R S H I S C M P G T V R R W N Y P S P L 1500

Figure 3F

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4501  TGCATTGCCACCTGTGGTGGGACACTGACCAGCATGAGTGGAGTGATCCTGAGCCCAGGC  4560
1501  C   I   A   T   C   G   G   T   L   T   S   M   S   G   V   I   L   S   P   G    1520

4561  TTCCCAGGGTCATACCCCAACAACCTGGACTGCACCTGGAAGATATCCCTGCCCATTGGC  4620
1521  F   P   G   S   Y   P   N   N   L   D   C   T   W   K   I   S   L   P   I   G    1540

4621  TATGGTGCACATATCCAATTTCTGAATTTCTCAACTGAAGCCAACCATGACTACCTGGAG  4680
1541  Y   G   A   H   I   Q   F   L   N   F   S   T   E   A   N   H   D   Y   L   E    1560

4681  ATCCAGAATGGCCCTTACCACAGTAGTCCAATGATGGGACAGTTCAGTGGCCCTGACCTG  4740
1561  I   Q   N   G   P   Y   H   S   S   P   M   M   G   Q   F   S   G   P   D   L    1580

4741  CCTGCGTCACTGCTGAGCACCACACATGAAACCCTCATCCGCTTCTATAGTGACCACTCA  4800
1581  P   A   S   L   L   S   T   T   H   E   T   L   I   R   F   Y   S   D   H   S    1600

4801  CAGAACCGACAAGGATTTAAACTCAGTTACCAAGCTTATGAGTTACAGAACTGCCCGGAC  4860
1601  Q   N   R   Q   G   F   K   L   S   Y   Q   A   Y   E   L   Q   N   C   P   D    1620

4861  CCACCCGCATTCCAGAATGGGTTCATGATCAACTCCGATTACAGCGTGGGCCAGTCGATC  4920
1621  P   P   A   F   Q   N   G   F   M   I   N   S   D   Y   S   V   G   Q   S   I    1640

4921  TCATTTGAGTGCTACCCGGGCTACATCTTGCTAGGCCACCCTGTGCTCACCTGCCAGCAT  4980
1641  S   F   E   C   Y   P   G   Y   I   L   L   G   H   P   V   L   T   C   Q   H    1660

4981  GGCACTGACAGGAACTGGAACTACCCTTTCCCACGGTGTGACGCTCCCTGTGGGTATAAT  5040
1661  G   T   D   R   N   W   N   Y   P   F   P   R   C   D   A   P   C   G   Y   N    1680

5041  GTGACATCACAGAATGGCACCATTTATTCCCCTGGGTTCCCAGACGAGTATCCAATTCTG  5100
1681  V   T   S   Q   N   G   T   I   Y   S   P   G   F   P   D   E   Y   P   I   L    1700

5101  AAGGACTGCCTGTGGCTGGTCACTGTCCCTCCAGGACATGGAGTGTACATCAACTTCACC  5160
1701  K   D   C   L   W   L   V   T   V   P   P   G   H   G   V   Y   I   N   F   T    1720

5161  TTGCTGCAGACTGAGGCTGTAAATGACTACATCGCTGTGTGGGATGGTCCTGACCAGAAC  5220
1721  L   L   Q   T   E   A   V   N   D   Y   I   A   V   W   D   G   P   D   Q   N    1740

5221  TCGCCTCAGCTCGGGGTCTTCAGTGGAAACACTGCCCTCGAGACAGCATACAGCTCCACC  5280
1741  S   P   Q   L   G   V   F   S   G   N   T   A   L   E   T   A   Y   S   S   T    1760

5281  AACCAGGTCTTGCTCAAATTCCACAGCGATTTCTCCAATGGAGGCTTCTTTGTCCTCAAT  5340
1761  N   Q   V   L   L   K   F   H   S   D   F   S   N   G   G   F   F   V   L   N    1780

5341  TTTCATGCATTTCAACTGAAGAGGTGCCCGCCTCCTCCAGTAGTGCCGCAGGCTGACCTG  5400
1781  F   H   A   F   Q   L   K   R   C   P   P   P   P   V   V   P   Q   A   D   L    1800

5401  CTTACAGAAGATGAAGACTTTGAAATAGGGGACTTCGTAAAGTACCAGTGCCATCCAGGG  5460
1801  L   T   E   D   E   D   F   E   I   G   D   F   V   K   Y   Q   C   H   P   G    1820

5461  TACACGCTGTTGGGAAGTGACACCCTGACATGCAAGCTCAGCTCACAGCTATTGTTCCAA  5520
1821  Y   T   L   L   G   S   D   T   L   T   C   K   L   S   S   Q   L   L   F   Q    1840

5521  GGCTCTCCACCTACCTGTGAAGCACAATGCCCAGCCAATGAAGTGCGAACAGAGTCTTCT  5580
1841  G   S   P   P   T   C   E   A   Q   C   P   A   N   E   V   R   T   E   S   S    1860

5581  GGGGTGATTCTCAGTCCTGGGTACCCAGGCAACTATTTTAACTCCCAGACATGTGCTTGG  5640
1861  G   V   I   L   S   P   G   Y   P   G   N   Y   F   N   S   Q   T   C   A   W    1880
```

Figure 3G

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5641  AGTATTAAAGTGGAGCCAAACTTTAACATTACGCTCTTTGTGGACACCTTTCAAAGTGAA  5700
1881  S  I  K  V  E  P  N  F  N  I  T  L  F  V  D  T  F  Q  S  E   1900

5701  AAGCAATTTGATGCACTGGAAGTATTTGATGGTTCTTCTGGGCAAAGTCCTTTGTTAGTG  5760
1901  K  Q  F  D  A  L  E  V  F  D  G  S  S  G  Q  S  P  L  L  V   1920

5761  GTCTTAAGTGGGAACCACACTGAACAGTCCAATTTTACCAGCAGAAGTAACCATCTGTAC  5820
1921  V  L  S  G  N  H  T  E  Q  S  N  F  T  S  R  S  N  H  L  Y   1940

5821  CTCCGCTGGTCCACAGATCATGCAACCAGCAAGAAAGGATTCAAGATTCGCTATGCAGCT  5880
1941  L  R  W  S  T  D  H  A  T  S  K  K  G  F  K  I  R  Y  A  A   1960

5881  CCTTACTGCAGCCTCACCTCTACACTCAAGAATGGTGGCGTTTTAAATAAAACCGCAGGC  5940
1961  P  Y  C  S  L  T  S  T  L  K  N  G  G  V  L  N  K  T  A  G   1980

5941  GCCCTGGGGAGCAAGGTGCAGTATTTCTGCAAGCCTGGATATCGAATGATTGGCCACAGC  6000
1981  A  L  G  S  K  V  Q  Y  F  C  K  P  G  Y  R  M  I  G  H  S   2000

6001  AACGCCACCTGCAGGCGGAACCCAGTGGGCGTGTACCAGTGGGACTCGATGGCACCGCTT  6060
2001  N  A  T  C  R  R  N  P  V  G  V  Y  Q  W  D  S  M  A  P  L   2020

6061  TGCCAGGCTGTGTCCTGTGGAATTCCAGAGGCTCCAGGAAATGGCTCGTTCACAGGCAAT  6120
2021  C  Q  A  V  S  C  G  I  P  E  A  P  G  N  G  S  F  T  G  N   2040

6121  GAGTTCACCTTAGACAGTAAAGTGACTTATGAATGTAATGAAGGCTTCAAGCTGGATGCC  6180
2041  E  F  T  L  D  S  K  V  T  Y  E  C  N  E  G  F  K  L  D  A   2060

6181  AGTCAGCAAGCCACTGCTGTGTGTCAAGAAGATGGCCTGTGGAGCAACAGAGGAAAGCCA  6240
2061  S  Q  Q  A  T  A  V  C  Q  E  D  G  L  W  S  N  R  G  K  P   2080

6241  CCCACGTGCAAACCGGTGCCCTGCCCCAGCATCGAAGGCCAGCTGTCAGAGCACGTGCTC  6300
2081  P  T  C  K  P  V  P  C  P  S  I  E  G  Q  L  S  E  H  V  L   2100

6301  TGGAGGCTGGTTTCGGGATCATTGAATGAATATGGAGCTCAAGTTCTCCTCAGCTGTAGT  6360
2101  W  R  L  V  S  G  S  L  N  E  Y  G  A  Q  V  L  L  S  C  S   2120

6361  CCTGGCTACTTCTTGCAGGGTCAGAGGCTGTTGCAGTGCCAAGCCAATGGGACCTGGAAC  6420
2121  P  G  Y  F  L  Q  G  Q  R  L  L  Q  C  Q  A  N  G  T  W  N   2140

6421  ACTGAGGAGGACAGACCCAGATGTAAAGTCATCTCCTGTGGAAGCCTGTCCTTTCCCCCA  6480
2141  T  E  E  D  R  P  R  C  K  V  I  S  C  G  S  L  S  F  P  P   2160

6481  AATGGTAACAAGATAGGGACGCTCACTATGTATGGAGCCACCGCCATCTTTACCTGCAAT  6540
2161  N  G  N  K  I  G  T  L  T  M  Y  G  A  T  A  I  F  T  C  N   2180

6541  ACCGGCTACACACTTGTAGGCTCCCATGTCCGGGAGTGCTTGGCCAATGGTCTCTGGAGC  6600
2181  T  G  Y  T  L  V  G  S  H  V  R  E  C  L  A  N  G  L  W  S   2200

6601  GGATCTGAAACAAGGTGCCTGGCGGGTCATTGTGGCTCTCCAGACCCCATTGTGAATGGC  6660
2201  G  S  E  T  R  C  L  A  G  H  C  G  S  P  D  P  I  V  N  G   2220

6661  CATATCAGTGGCGATGGCTTCAGCTACAGGGACACAGTGGTCTACCAATGCAACCCTGGG  6720
2221  H  I  S  G  D  G  F  S  Y  R  D  T  V  V  Y  Q  C  N  P  G   2240

6721  TTTCGACTCGTAGGCACGTCTGTGAGGATTTGCCTGCAGGACCACAAGTGGTCGGGGCAG  6780
2241  F  R  L  V  G  T  S  V  R  I  C  L  Q  D  H  K  W  S  G  Q   2260
```

Figure 3H

```
6781 ACCCCCGTTTGCGTCCCCATCACATGTGGACACCCTGGAAACCCTGCCCATGGCCTCACC 6840
2261 T  P  V  C  V  P  I  T  C  G  H  P  G  N  P  A  H  G  L  T   2280

6841 AACGGCAGCGAGTTCAACCTGAATGACCTTGTGAATTTCACCTGCCATACGGGCTACCTG 6900
2281 N  G  S  E  F  N  L  N  D  L  V  N  F  T  C  H  T  G  Y  L   2300

6901 CTGCAGGGTGCCTCCCGAGCCCAATGTCGGAGCAACGGCCAGTGGAGCAGCCCCTTGCCT 6960
2301 L  Q  G  A  S  R  A  Q  C  R  S  N  G  Q  W  S  S  P  L  P   2320

6961 ATCTGCCGAGTGGTGAACTGTTCCGATCCTGGATTTGTGGAAAATGCAGTTCGCCACGGG 7020
2321 I  C  R  V  V  N  C  S  D  P  G  F  V  E  N  A  V  R  H  G   2340

7021 CAACAGAACTTTCCAGAGAGTTTCGAGTATGGGACAAGTGTGATGTATCACTGCAAGAAG 7080
2341 Q  Q  N  F  P  E  S  F  E  Y  G  T  S  V  M  Y  H  C  K  K   2360

7081 GGGTTCTACCTACTGGGCTCTTCTGCCCTGACCTGCATGGCAAGTGGCTTGTGGGACCGC 7140
2361 G  F  Y  L  L  G  S  S  A  L  T  C  M  A  S  G  L  W  D  R   2380

7141 TCCTTACCCAAGTGTCTGGCTATATCATGTGGGCATCCTGGGGTCCCCGCTAATGCTGTC 7200
2381 S  L  P  K  C  L  A  I  S  C  G  H  P  G  V  P  A  N  A  V   2400

7201 CTGACTGGAGAATTGTTTACATTTGGAGCCACAGTTCAGTACTCCTGCAAAGGGGGCCAG 7260
2401 L  T  G  E  L  F  T  F  G  A  T  V  Q  Y  S  C  K  G  G  Q   2420

7261 ATTCTCACAGGCAATAGCACAAGAGTCTGCCAAGAAGACAGTCACTGGAGTGGATCCCTT 7320
2421 I  L  T  G  N  S  T  R  V  C  Q  E  D  S  H  W  S  G  S  L   2440

7321 CCCCATTGTTCAGGAAATAGTCCTGGATTTTGTGGTGATCCAGGGACCCCAGCACATGGG 7380
2441 P  H  C  S  G  N  S  P  G  F  C  G  D  P  G  T  P  A  H  G   2460

7381 TCTCGTCTTGGGGATGAGTTTAAGACAAAGAGTCTTTTGCGATTCTCCTGTGAGATGGGC 7440
2461 S  R  L  G  D  E  F  K  T  K  S  L  L  R  F  S  C  E  M  G   2480

7441 CACCAGCTGCGGGGTTCTGCAGAGCGCACATGCCTGGTGAATGGGTCCTGGTCAGGAGTC 7500
2481 H  Q  L  R  G  S  A  E  R  T  C  L  V  N  G  S  W  S  G  V   2500

7501 CAGCCTGTGTGTGAGGCCGTGTCCTGTGGAAACCCTGGCACCCCTACCAATGGGATGATC 7560
2501 Q  P  V  C  E  A  V  S  C  G  N  P  G  T  P  T  N  G  M  I   2520

7561 CTCAGCAGCGATGGAATCCTCTTCTCCAGCTCTGTCATCTATGCCTGCTGGGAAGGCTAC 7620
2521 L  S  S  D  G  I  L  F  S  S  S  V  I  Y  A  C  W  E  G  Y   2540

7621 AAGACCTCGGGGCTCATGACGCGGCACTGCACAGCGAACGGGACATGGACAGGCACAGCC 7680
2541 K  T  S  G  L  M  T  R  H  C  T  A  N  G  T  W  T  G  T  A   2560

7681 CCTGACTGTACAATCATCAGCTGTGGTGATCCTGGCACACTGCCCAATGGCATCCAGTTT 7740
2561 P  D  C  T  I  I  S  C  G  D  P  G  T  L  P  N  G  I  Q  F   2580

7741 GGGACAGACTTCACTTTCAACAAGACCGTGAGCTATCAGTGCAACCCTGGCTACCTGATG 7800
2581 G  T  D  F  T  F  N  K  T  V  S  Y  Q  C  N  P  G  Y  L  M   2600

7801 GAGCCCCCAACATCACCCACCATCCGCTGCACCAAAGATGGTACATGGAATCAGACCCGG 7860
2601 E  P  P  T  S  P  T  I  R  C  T  K  D  G  T  W  N  Q  T  R   2620

7861 CCCCTCTGCAAAGCTGTTCTATGCAGCCAGCCTCCCTCAGTGCCAAACGGAAAGGTGGAG 7920
2621 P  L  C  K  A  V  L  C  S  Q  P  P  S  V  P  N  G  K  V  E   2640
```

Figure 3I

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7921  GGGTCAGACTTCCGATGGGGTGCCAGCATAAGCTACAGTTGTGTGGATGGCTACCAGCTC  7980
2641  G  S  D  F  R  W  G  A  S  I  S  Y  S  C  V  D  G  Y  Q  L   2660

7981  TCCCACTCGGCCATCCTGTCCTGTGAAGGGCGTGGAGTATGGAAAGGAGAAGTCCCTCAG  8040
2661  S  H  S  A  I  L  S  C  E  G  R  G  V  W  K  G  E  V  P  Q   2680

8041  TGCTTGCCTGTGTTCTGTGGCGATCCAGGCACTCCAGCAGAGGGACGGCTCAGTGGGAAA  8100
2681  C  L  P  V  F  C  G  D  P  G  T  P  A  E  G  R  L  S  G  K   2700

8101  AGCTTCACCTTTAAGTCTGAGGTCTTCATCCAGTGCAAACCCCCATTTGTGTTAGTGGGT  8160
2701  S  F  T  F  K  S  E  V  F  I  Q  C  K  P  P  F  V  L  V  G   2720

8161  TCCTCGAGGAGAACCTGCCAGGCCGATGGGATGTGGAGTGGCATCCAGCCCACTTGTATA  8220
2721  S  S  R  R  T  C  Q  A  D  G  M  W  S  G  I  Q  P  T  C  I   2740

8221  GATCCAGCCCACACCGCTTGCCCAGACCCCGGCACTCCCCACTTTGGAATACAGAATAGC  8280
2741  D  P  A  H  T  A  C  P  D  P  G  T  P  H  F  G  I  Q  N  S   2760

8281  TCGAAAGGATACGAGGTTGGAAGCACTGTGTTCTTCAGATGTAGAAAAGGTTACCACATC  8340
2761  S  K  G  Y  E  V  G  S  T  V  F  F  R  C  R  K  G  Y  H  I   2780

8341  CAAGGCTCCACTACCCGGACCTGTCTTGCCAACCTCACGTGGAGTGGAATCCAGACAGAG  8400
2781  Q  G  S  T  T  R  T  C  L  A  N  L  T  W  S  G  I  Q  T  E   2800

8401  TGCATCCCCCATGCCTGCCGGCAGCCAGAGACCCCAGCGCATGCAGATGTGAGAGCCATC  8460
2801  C  I  P  H  A  C  R  Q  P  E  T  P  A  H  A  D  V  R  A  I   2820

8461  GATCTTCCAGCTTTTGGCTACACCTTAGTCTACACCTGTCATCCAGGATTTTTCCTTGCT  8520
2821  D  L  P  A  F  G  Y  T  L  V  Y  T  C  H  P  G  F  F  L  A   2840

8521  GGCGGATCTGAGCACAGGACGTGTAAAGCAGACATGAAATGGACAGGAAAGTCACCTGTT  8580
2841  G  G  S  E  H  R  T  C  K  A  D  M  K  W  T  G  K  S  P  V   2860

8581  TGTAAAAGTAAAGGAGTGAGAGAAGTTAATGAAACAGTTACTAAAACTCCAGTTCCTTCT  8640
2861  C  K  S  K  G  V  R  E  V  N  E  T  V  T  K  T  P  V  P  S   2880

8641  GATGTATTTTTCATCAACTCGGTGTGGAAGGGATATTATGAATATTTAGGCAAGAGACAG  8700
2881  D  V  F  F  I  N  S  V  W  K  G  Y  Y  E  Y  L  G  K  R  Q   2900

8701  CCGGCGACTCTCACTGTGGACTGGTTTAATGCAACCAGCAGCAAGGTCAATGCGACCTTC  8760
2901  P  A  T  L  T  V  D  W  F  N  A  T  S  S  K  V  N  A  T  F   2920

8761  ACCGCAGCCTCACAGGTGCAGCTGGAGCTGACAGGGGTCTACAAGAAGGAAGAGGCCCAC  8820
2921  T  A  A  S  Q  V  Q  L  E  L  T  G  V  Y  K  K  E  E  A  H   2940

8821  CTGCTTCTGAAAGCCTTTCATATCAAAGGCCCAGCAGATATTTTTGTAAGCAAGTTTGAA  8880
2941  L  L  L  K  A  F  H  I  K  G  P  A  D  I  F  V  S  K  F  E   2960

8881  AATGACAACTGGGGACTCGATGGTTATGTATCCTCAGGACTTGAGAGAGGAGGATTCTCC  8940
2961  N  D  N  W  G  L  D  G  Y  V  S  S  G  L  E  R  G  G  F  S   2980

8941  TTTCAGGGTGATATACATGGAAAAGACTTCGGGAAGTTCAAGCTGGAAAGACAAGATCCT  9000
2981  F  Q  G  D  I  H  G  K  D  F  G  K  F  K  L  E  R  Q  D  P   3000

9001  TCCAACTCTGATGCAGATTCTTCAAATCATTACCAGGGCACCAGCAGTGGCTCTGTGGCA  9060
3001  S  N  S  D  A  D  S  S  N  H  Y  Q  G  T  S  S  G  S  V  A   3020
```

Figure 3J

9061 GCTGCGATTCTCGTCCCCTTCTTCGCTCTAATTCTATCAGGGTTTGCATTTTACCTCTAC 9120
3021 A A I L V P F F A L I L S G F A F Y L Y 3040

9121 AAACACAGAACAAGACCAAAAGTTCAATACAATGGCTATGCTGGCCATGAAAACAGTAAT 9180
3041 K H R T R P K V Q Y N G Y A G H E N S N 3060

9181 GGACAAGCTTCATTTGAAAACCCCATGTATGATACAAACTTAAAACCCACAGAGGCCAAG 9240
3061 G Q A S F E N P M Y D T N L K P T E A K 3080

9241 GCTGTGAGGTTTGACACGACTCTGAACACAGTGTGTACAGTGGTATAGCCCTCAGTGCCC 9300
3081 A V R F D T T L N T V C T V V * 3096

9301 CCTAGGACCGACTCATAGCCATACCTCTGATGGACAAGCAGTAAAATCCTTTGGTGCCAT 9360
9361 ATACCACCCCCTTCTACTCTTACCTTGCTGCAGCAACGTTGGCCATCGTCTGCTGGCATA 9420
9421 ACGCAGTGGGAATGTCTTCTCCATCATGCCCGAGTCTTCTGAGGATCAAATTGCAAATAC 9480
9481 ACCTTCATCTGGAAAGTGGCTTATAAAAAGCCCGGTTGCTGCATCCACCAGAAATCAAGA 9540
9541 CCCCGACAACAGCGAGGGCAAGGAAGACTGCAGAGTCTCCCAGACCGGTGGTACTTAATG 9600
9601 CCTCTGACTTTTGTGTCTCTGTGTGGCCAGGATGCCTTTGGTGTAGTCTTCTGAGCACAC 9660
9661 CGATACATCCCTCAGGTGCGGCGACAACATGGTAGCCACTTGATGTGTGTTTTGTGTTTT 9720
9721 TCTGTTTTCTTTTCAACCCTATCCACTGGACATGAATTCTTTACAAAAGAAAAGCCTTCC 9780
9781 TGGAGAAGACGCCTTCTGGAAAATGCACACACAGACGCTTTGCTTCTGCCCTGCCTGAGA 9840
9841 CAGGAGCTCTCCGGATCTTCAGGCTCCACTGGGCGTCCATCAGCCACTAGGGATGTTTGC 9900
9901 AGATCTCACAGTCAGAGCTGGTCCATCCCAGAGTTTTTGATGCTCAACATTTTGCACTA 9960
9961 GTGTGTCAAGAATGACTAAGTCTGATTTCTAAACAAACTATTTCCACAGGGTTTGTATCC 10020
10021 ACTATACATTGTACATACGCATTTTCTCATACCGTATTCTCAAGCAAATGATGCCACTGT 10080
10081 CAGTTAAGTTTGGGATGCAAAGGAAGGTCTCCCCGGATACAGAACAGATTTTGAAAAGGA 10140
10141 GATAGTGCTAGTAATGCTGAAGAAGTTACTCTTTTAATTGCTTCTGTTGGCCACATTTTC 10200
10201 ATGTCAAATTCATTGCCTACTTCCAGTGGTGGAAATGAAGCCCGTGTATTCCCCTTGGTA 10260
10261 TCCCCCCACTTCATGTGCATACGACTATTGTCTACACCATACTAATCAATAACAGGGGGC 10320
10321 TCCAGCAATGTCTGTTTTCCATGTACAGATGTGAATAGTAATTTATTTTAGGTAGCTCAT 10380
10381 GAACTCAGTTCACAGTGAAGTCTTCCCTTCCGGATTGTTTCCTTTCTCTGTTTTGTAACA 10440
10441 TCACCCTCCCAGAATGCATTGAGAGTCTATCTCACAGCCACACCCAAGCTCAGAGGAATC 10500
10501 GAAAGGGAAATCAAAGAAGTCCAAATCAGAATCGGAAGGGCAGGCACCGCTCGCACACCC 10560
10561 TCATGATGATCTGTTTTATAGATTATTTGCCTTTCTGCAAAAAAAAAATCATTACAGTGA 10620
10621 TTTTTGAAACATTAAAATTCCTTACTGATAGACTATCTATTGTGATATATATAAGATAGG 10680
10681 TGGTATGGCCAACAGGGATAAAATAAACAGCCTAAAGACAAGGCAGGGCTAGAGAAATGT 10740
10741 CTGTAAGAAATTTCAAAGAGAAGATCATGTTTATTTTTATTTATATTTGTTTGATAAAAG 10800
10801 TATTTTTGGAAATATAATGCTTATTTTATTATTTGACGTTTCATGCACAGTCCACGTGGT 10860
10861 AAAAATCCCCCCTTTGTACATCCCAGATTTGCACTGATACATGGGTCAGGATGTCATGCT 10920
10921 GATGTTCTGTTTGCTGTGGTGACTACATTCATGCCTAGCTTTAAGACAGGTGGATCTGTC 10980
10981 TATCTACATGATGTTTAAATGCAGGACTTCCCAGAGGACAGTGGGTAACGGAACATGGCT 11040
11041 TGCTTGCGGCTTTGGAAGTTCAGCATTCTGAGCGTTCCAGAGGCCCGGCTGGGCTCCCTC 11100
11101 CTTCTAGCCCACTGTTCTTGCAAGGGCTGTCTGTTGTGTGCCAGGGCTCCTGACTTCTTC 11160
11161 TGCTGACACTCTGTCCACTGGGTTCCATATTCCAGGACTCCATGTCCTAGGAAAGAGTTT 11220
11221 TGACATAGGTTCCTCCAGCCAAGCCGACACACATCCACGGGGTTCCTCTGGGCTCCACAG 11280
11281 AGGTTCTTCATTGGCTCCCTGGGATAAATTCAGATGATGTCAGCAAGAGTGTGCTTCTAT 11340
11341 ACCACACATTGAGCCAAAACAAAACAGAGAACGTCAGAAGGTCCACGGACCAGAGTGCGC 11400
11401 AAGGGAGAACAGGGTTACTATATATATTAGATGTATATAAAAACACACACACAAACATAT 11460
11461 ATATATTGTACATATCTAAGTTTGAGTCACTCAGACTAGGTGCAAAATGCTGACTTTGGA 11520
11521 GTCTAAACTAACGTCTCTGTCCCCACATCCCTGGCCTCTTTCCTGGCCAGTTACATTAAG 11580
11581 AAGACTTGACTTAGACAGGGCATACATACATGCAAGGAACCACATCATCAGACCAGTGTC 11640
11641 GTTTTCCTTTGTGTGCAAACTGACCTACAGCTACCAGACTGCATCATGGTATTTAAAACC 11700
11701 AACATACAATATTGAGCGGCACTCTCAGTTGAGAGCCTAGCTCAATCCTTCCTAGGANNN 11760
11761 NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN 11820
11821 NNNNNNNNCACCAGGTCTCAGAGGCATTGAAGACCTAGCAGGACAGTCAGGAACACCTTC 11880
11881 CTCAGTGAGGTCTAGACTTTTCCCTGAAGCGCCCAGAGCACAGTGAGGAGTCACGCTCTA 11940
11941 TGAATGACAGGTTATGTGCTTTGAAGCTGTTCAACTGTTGCTTGTCTTTGCCCATCTTGC 12000

Figure 3K

12001 CTTCAGGCTAGCTGCAATAATTTTTTTCTTCTGTAAAATATTTTGTAAACAATAACAACA 12060
12061 ACAACAAAAGCTATTATAAAAAGGGAGAAAAGAAAGCTGGCATTATGATCAGGAAAACCA 12120
12121 TCCATTCTTGCTGCCCCCCCCCCCTCCTGTCTCCACCACGCTGCTGTCACAACGTAGGTG 12180
12181 CGGAAGACCTTTTTGTACAGAGATATATTTTTTATGAAGAATTTGTAAAATTATTAAATA 12240
12241 TGCTGTAATTTTTTGATTAATGTAGGTAAATTGTTAAAAAATAAATGTTTTTACAATATG 12300
12301 AAACTGTAATTTTCCCCCATAATGTAACATTACCCTCTCTAGCTGATTTTCAGTTCCAAT 12360
12361 CCTATTCGAACATGTATTAATATTAAGGCGGCCTGTTAAAATGAACAGTATCTTTTTTTT 12420
12421 TGTCAAAAAAAATTATAAAGAGAGTGTAACATAACCTGTGTAATGCCACCTATCTTTAAA 12480
12481 GCAAATCAGAGTTCTAATTAAATATTTAATTTAGATTTCAAAAA 12525

Figure 4A

Comparison of Human C3b/C4b Complement Receptor, "h-CR" (SEQ ID NO:5) and Human AGP-41773, "41773" (SEQ ID NO:2)

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h-CR   102 KSCRNPPDPVNGMVHVIKGIQFGSQIKYSCTKGYRLIGSSSATCIISGDT 151
41773  293 QNCPDPPPFQNGYM.INSDYSVGQSVSFECYPGYILIGHPVLTC.QHGIN 340

       152 VIWDNETPICDRIPCGLPPTITNGDFISTNRENFH...YGSVVTYRCNPG 198
       341 RNWNYPFPRCD.APCGYNVTSQNGTIYSPGFPDEYPILKDCIWLITVPPG 389

       199 SGGRKVFELVGEPSIYCTSNDDQVGIWSGP...APQCIIPNKCTPPNVEN 245
       390 HGVYINFTLLQTEAV.....NDYIAVWDGPDQNSPQLGVFSGNTA..LET 432

       246 GILVSDNRSLFSLNEVVEFRCQPGFVMKGPRRVKCQALNKWEPELPSCSR 295
       433 A.YSSTNQVLLKFHS..DF.SNGGFFV..........LNFHAFQL....K 464

       296 VCQPPPDVLHAERTQRDKDNFSPGQEVFYSCEPGYDLRGAASMRC..TPQ 343
       465 KCQPPPAVPQAEMLTED.DDFEIGDFVKYQCHPGYTLVGTDILTCKLSSQ 513

       344 GDWSPAAPTCEVKS..............CDDFMGQLLNGR.....VLFPV 374
       514 LQFEGSLPTCEAQCPANEVRTGSSGVILSPGYPGNYFNSQTCSWSIKVEP 563

       375 NLQLGAKVD.FVCDEGFQL.......KGSSASYCVLAGMES......... 407
       564 NYNITIFVDTFQSEKQFDALEVFDGSSGQSPLLVVLSGNHTEQSNFTSRS 613

       408 .....LWNSSVPVCEQIF........CPSPPVIPNGRHTGKPLEVFPFGK 444
       614 NQLYLRWSTDHATSKKGFKIRYAAPYCSLTHPLKNGGILNRTAGA..VGS 661

       445 AVNYTCDPHPDRGTSFDLIGESTIRCTSDPQGNGVWSSPAPRCGILGHCQ 494
       662 KVHYFCKP......GYRMVGHSNATCRRNPLGMYQWDSLTPLCQAVS.CG 704

       495 APDHFLFAKLKTQTNASDFPIGTSLKYECRPEY...YGRPFSITCLDNLV 541
       705 IPE....SPGNGSFTGNEFTLDSKVVYECHEGFKLESSQQATAVCQEDGL 750

       542 WSS..PKDVCKRKSCKTPPDPVNGMVHVITDI......QVGSRINYSCTT 583
       751 WSNKGKPPTCKPVAC..PSIEAQLSEHVIWRLVSGSLNEYGAQVLLSCSP 798

       584 GHRLIGHSSAECILSGNAAHWS..TKPPICQRIPCGLPPTIANGDFISTN 631
       799 GYYLEGWRLLRCQANGT...WNIGDERPSCRVISCGSLSFPPNGNKIGTL 845

       632 RENFHYGSVVTYRCNPGSGGRKVFELVGEPSIYCTSNDDQVGIWSGPAPQ 681
       846 TV...YGATAIFTCNTG.....YTLVGSHVRECLAN...GLWSGSETR 882
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Figure 4B

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 682 CIXPNKCTPPNVENGILVSDNRSLFSLNEVVEFRCQPGFVMKGPRRVKCQ 731
 883 CLAGHCGSPDPIVNGHISGDG...FSYRDTVVYQCNPGFRLVGTSVRICL 929

 732 ALNKWEPELPSCSRV.CQPPPDVLHAERTQRDKDNFSPGQEVFYSCEPGY 780
 930 QDHKWSGQTPVCVPITCGHPGNPAHG...FTNGSEFNLNDVVNFTCNTGY 976

 781 DLRGAASMRCTPQGDWSPAAPTCEVKSCDD..FM.GQLLNGRVLFPVNLQ 827
 977 LLQGVSRAQCRSNGQWSSPLPTCRVVNCSDPGFVENAIRHGQQNFPESFE 1026

 828 LGAKVDFVCDEGFQLKGSSASYCVLAGMESLWNSSVPVCEQIFCPSPPVI 877
1027 YGMSILYHCKKGFYLLGSSALTCMANG...LWDRSLPKCLAISCGHPGVP 1073

 878 PNGRHTGKPLEVFPFGKTVNYTCDPHPDRGTSFDLIGESTIRCTSDPQGN 927
1074 ANAVLTG...ELFTYGAVVHYSC.....RG.SESLIGNDTRVCQEDSH.. 1112

 928 GVWSSPAPRC.....GILGHCQAPDHFLFAKLKTQTNASDFPIGTSLKYE 972
1113 ..WSGALPHCTGNNPGFCGDPGTPAH..GSRL.....GDDFKTKSLLRFS 1153

 973 CR..PEYYGRPFSITCLDNLVWSSPKDVCKRKSCKTPPDPVNGMVHVITD 1020
1154 CEMGHQLRGSP.ERTCLLNGSWSGLQPVCEAVSCGNPGTPTNGMIVSSDG 1202

1021 IQVGSRINYSCTTGHRLIGHSSAECILSGNAAHWSTKPPICQRIPCGLPP 1070
1203 ILFSSSVIYACWEGYKTSGLMTRHCTANGT...WTGTAPDCTIISCGDPG 1249

1071 TIANGDFISTNRENFHYGSVVTYRCNPGSGGRKVFELVGEPSIYCTSNDD 1120
1250 TLANGIQFGT...DFTFNKTVSYQCNPG....YVMEAVTSATIRCTKD.. 1290

1121 QVGIWSGPAPQCIXPNKCTPPNVENGILVSDNRSLFSLNEVVEFRCQPGF 1170
1291 ..GRWNPSKPVCKAVLCPQPPPVQNGTVEGSD...FRWGSSISYSCMDGY 1335

1171 VMKGPRRVKCQALNKWEPELPSCSRV.CQPPPDVLHAERTQRDKDNFSPG 1219
1336 QLSHSAILSCEGRGVWKGEIPQCLPVFCGDPG..IPAEGRLSGK.SFTYK 1382

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1383 SEVFFQCKSPFILVGSSRRVCQADGTWSGIQPTCIDPAHNTCPD.PGTPH 1431

1267 NGRVLFPVNLQLGAKVDFVCDEGFQLKGSSASYCVLAGMESLWNSSVPVC 1316
1432 FGIQNSSRGYEVGSTVFFRCRKGYHIQGSTTRTC.LANL..TWSGIQTEC 1478
```

Figure 4C

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          .         .         .         .         .
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         |  |   |      : ::.  ||  . |||  ||     | | | |
1479 IPHACRQPET.P.AHADVRAIDLPTFGYTLVYTC..HP....GFFLAGGS 1520

              .         .
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SEQUENCE LISTING

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<120> C3B/C4B COMPLEMENT RECEPTOR-LIKE MOLECULES AND USES THEREOF

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<141> 2001-07-23

<150> 09/728,787

<141> 2000-11-28

<150> US 60/222,504

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Val Glu Pro Gln Phe Asp Phe Leu Ala Val Lys Asp Asp Gly Ile Ser
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Asp Ile Thr Val Leu Gly Thr Phe Ser Gly Asn Glu Val Pro Ser Gln
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Asp Arg Phe Leu Leu Gly Ser Ser Val Ser Phe His Cys Asp Asp Gly
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ggg aac gtg gtc tgg agc tcc acc gtg ccc cgc tgt gaa gct cca tgt      1122
Gly Asn Val Val Trp Ser Ser Thr Val Pro Arg Cys Glu Ala Pro Cys
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ggt gga cat ctg aca gcg tcc agc gga gtc att ttg cct cct gga tgg      1170
Gly Gly His Leu Thr Ala Ser Ser Gly Val Ile Leu Pro Pro Gly Trp
    265                 270                 275

cca gga tat tat aag gat tct tta cat tgt gaa tgg ata att gaa gca      1218
Pro Gly Tyr Tyr Lys Asp Ser Leu His Cys Glu Trp Ile Ile Glu Ala
280                 285                 290                 295

aaa cca ggc cac tct atc aaa ata act ttt gac aga ttt cag aca gag      1266
Lys Pro Gly His Ser Ile Lys Ile Thr Phe Asp Arg Phe Gln Thr Glu
                300                 305                 310

gtc aat tat gac acc ttg gag gtc aga gat ggg cca gcc agt tcg tcc      1314
Val Asn Tyr Asp Thr Leu Glu Val Arg Asp Gly Pro Ala Ser Ser Ser
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cca ctg atc ggc gag tac cac ggc acc cag gca ccc cag ttc ctc atc      1362
Pro Leu Ile Gly Glu Tyr His Gly Thr Gln Ala Pro Gln Phe Leu Ile
        330                 335                 340

agc acc ggg aac ttc atg tac ctg cta ttc acc act gac aac agc cgc      1410
Ser Thr Gly Asn Phe Met Tyr Leu Leu Phe Thr Thr Asp Asn Ser Arg
    345                 350                 355

tcc agc atc ggc ttc ctc atc cac tat gag agt gtg acg ctt gag tcg      1458
Ser Ser Ile Gly Phe Leu Ile His Tyr Glu Ser Val Thr Leu Glu Ser
360                 365                 370                 375

gat tcc tgc ctg gac ccg ggc atc cct gtg aac grc cat cgc cac ggt      1506
Asp Ser Cys Leu Asp Pro Gly Ile Pro Val Asn Xaa His Arg His Gly
                380                 385                 390

gga gac ttt ggc atc agg tcc aca gtg act ttc agc tgt gac ccg ggg      1554
Gly Asp Phe Gly Ile Arg Ser Thr Val Thr Phe Ser Cys Asp Pro Gly
            395                 400                 405

tac aca cta agt gac gac gag ccc ctc gtc tgt gag agg aac cac cag      1602
Tyr Thr Leu Ser Asp Asp Glu Pro Leu Val Cys Glu Arg Asn His Gln
        410                 415                 420

tgg aac cac gcc ttg ccc agc tgc gac gct cta tgt gga ggc tac atc      1650
Trp Asn His Ala Leu Pro Ser Cys Asp Ala Leu Cys Gly Gly Tyr Ile
    425                 430                 435

caa ggg aag agt gga aca gtc ctt tct cct ggg ttt cca gat ttt tat      1698
Gln Gly Lys Ser Gly Thr Val Leu Ser Pro Gly Phe Pro Asp Phe Tyr
440                 445                 450                 455

cca aac tct cta aac ygc acg tgg acc att gaa gtg tct cat ggg aaa      1746
Pro Asn Ser Leu Asn Xaa Thr Trp Thr Ile Glu Val Ser His Gly Lys
                460                 465                 470

gga gtt caa atg atc ttt cac acc ttt cat ctt gag agt tcc cac gac      1794
Gly Val Gln Met Ile Phe His Thr Phe His Leu Glu Ser Ser His Asp
            475                 480                 485
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tat tta ctg atc aca gag gat gga agt ttt tcc gag ccc gtt gcc agg      1842
Tyr Leu Leu Ile Thr Glu Asp Gly Ser Phe Ser Glu Pro Val Ala Arg
        490                 495                 500

ctc acc ggg tcg gtg ttg cct cat acg atc aag gca ggc ctg ttt gga      1890
Leu Thr Gly Ser Val Leu Pro His Thr Ile Lys Ala Gly Leu Phe Gly
    505                 510                 515

aac ttc act gcc cag ctt cgg ttt ata tca gac ttc tca att tcg tac      1938
Asn Phe Thr Ala Gln Leu Arg Phe Ile Ser Asp Phe Ser Ile Ser Tyr
520                 525                 530                 535

gag ggc ttc aat atc aca ttt tca gaa tat gac ctg gag cca tgt gat      1986
Glu Gly Phe Asn Ile Thr Phe Ser Glu Tyr Asp Leu Glu Pro Cys Asp
                540                 545                 550

gat cct gga gtc cct gcc ttc agc cga aga att ggt ttt cac ttt ggt      2034
Asp Pro Gly Val Pro Ala Phe Ser Arg Arg Ile Gly Phe His Phe Gly
            555                 560                 565

gtg gga gac tct ctg acg ttt tcc tgc ttc ctg gga tat cgt tta gaa      2082
Val Gly Asp Ser Leu Thr Phe Ser Cys Phe Leu Gly Tyr Arg Leu Glu
        570                 575                 580

ggt gcc rcc aag ctt acc tgc ctg ggt ggg ggc cgc cgt gtg tgg agt      2130
Gly Ala Xaa Lys Leu Thr Cys Leu Gly Gly Gly Arg Arg Val Trp Ser
    585                 590                 595

gca cct ctg cca agg tgt gtg gcc gaa tgt gga gca agt gtc aaa gga      2178
Ala Pro Leu Pro Arg Cys Val Ala Glu Cys Gly Ala Ser Val Lys Gly
600                 605                 610                 615

aat gaa gga aca tta ctg tct cca aat ttt cca tcc aat tat gat aat      2226
Asn Glu Gly Thr Leu Leu Ser Pro Asn Phe Pro Ser Asn Tyr Asp Asn
                620                 625                 630

aac cat gag tgt atc tat aaa ata gaa aca gaa gcc ggc aag ggc atc      2274
Asn His Glu Cys Ile Tyr Lys Ile Glu Thr Glu Ala Gly Lys Gly Ile
            635                 640                 645

cac ctt aga aca cga agc ttc cag ctg ttt gaa gga gat act cta aag      2322
His Leu Arg Thr Arg Ser Phe Gln Leu Phe Glu Gly Asp Thr Leu Lys
        650                 655                 660

gta tat gat gga aaa gac agt tcc tca cgt cca ctg ggc acg ttc act      2370
Val Tyr Asp Gly Lys Asp Ser Ser Ser Arg Pro Leu Gly Thr Phe Thr
    665                 670                 675

aaa aat gaa ctt ctg ggg ctg atc cta aac agc aca tcc aat cac ctr      2418
Lys Asn Glu Leu Leu Gly Leu Ile Leu Asn Ser Thr Ser Asn His Xaa
680                 685                 690                 695

tgg cta gag ttc aac acc aat gga tct gac acc gac caa ggt ttt caa      2466
Trp Leu Glu Phe Asn Thr Asn Gly Ser Asp Thr Asp Gln Gly Phe Gln
                700                 705                 710

ctc acc tat acc agt ttt gat ctg gta aaa tgt gag gat ccg ggc atc      2514
Leu Thr Tyr Thr Ser Phe Asp Leu Val Lys Cys Glu Asp Pro Gly Ile
            715                 720                 725
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cct aac tac ggc tat agg atc cgt gat gaa ggc cac ttt acc gac act      2562
Pro Asn Tyr Gly Tyr Arg Ile Arg Asp Glu Gly His Phe Thr Asp Thr
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gta gtt ctg tac agt tgc aac ccg ggg tac gcc atg cat ggc agc aac      2610
Val Val Leu Tyr Ser Cys Asn Pro Gly Tyr Ala Met His Gly Ser Asn
    745                 750                 755

acc ctg acc tgt ttg agt gga gac agg aga gtg tgg gac aaa cca cta      2658
Thr Leu Thr Cys Leu Ser Gly Asp Arg Arg Val Trp Asp Lys Pro Leu
760                 765                 770                 775

cct tcg tgc ata gcg gaa tgt ggt ggt cag atc cat gca gcc aca tca      2706
Pro Ser Cys Ile Ala Glu Cys Gly Gly Gln Ile His Ala Ala Thr Ser
                780                 785                 790

gga cga ata ttg tcc cct ggc tat cca gct ccg tat gac aac aac ctc      2754
Gly Arg Ile Leu Ser Pro Gly Tyr Pro Ala Pro Tyr Asp Asn Asn Leu
            795                 800                 805

cac tgc acc tgg att ata gag gca gac cca gga aag acc att agc ctc      2802
His Cys Thr Trp Ile Ile Glu Ala Asp Pro Gly Lys Thr Ile Ser Leu
        810                 815                 820

cat ttc att gtt ttc gac acg gag atg gct cac gac atc ctc aag gtc      2850
His Phe Ile Val Phe Asp Thr Glu Met Ala His Asp Ile Leu Lys Val
    825                 830                 835

tgg gac ggg ccg gtg gac agt gac atc ctg ctg aag gag tgg agt ggc      2898
Trp Asp Gly Pro Val Asp Ser Asp Ile Leu Leu Lys Glu Trp Ser Gly
840                 845                 850                 855

tcc gcc ctt ccg gag gac atc cac agc acc ttc aac tca ctc acc ctg      2946
Ser Ala Leu Pro Glu Asp Ile His Ser Thr Phe Asn Ser Leu Thr Leu
                860                 865                 870

cag ttc gac agc gac ttc ttc atc agc aag tct ggc ttc tcc atc cag      2994
Gln Phe Asp Ser Asp Phe Phe Ile Ser Lys Ser Gly Phe Ser Ile Gln
            875                 880                 885

ttc tcc acc tca att gca gcc acc tgt aac gat cca ggt atg ccc caa      3042
Phe Ser Thr Ser Ile Ala Ala Thr Cys Asn Asp Pro Gly Met Pro Gln
        890                 895                 900

aat ggc acc cgc tat gga gac agc aga gag gct gga gac acc gtc aca      3090
Asn Gly Thr Arg Tyr Gly Asp Ser Arg Glu Ala Gly Asp Thr Val Thr
    905                 910                 915

ttc cag tgt gac cct ggc tat cag ctc caa gga caa gcc aaa atc acc      3138
Phe Gln Cys Asp Pro Gly Tyr Gln Leu Gln Gly Gln Ala Lys Ile Thr
920                 925                 930                 935

tgt gtg cag ctg aat aac cgg ttc ttt tgg caa cca gac cct cct aca      3186
Cys Val Gln Leu Asn Asn Arg Phe Phe Trp Gln Pro Asp Pro Pro Thr
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tgc ata gct gct tgt gga ggg aat ctg acg ggc cca gca ggt gtt att      3234
Cys Ile Ala Ala Cys Gly Gly Asn Leu Thr Gly Pro Ala Gly Val Ile
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Leu Ser Pro Asn Tyr Pro Gln Pro Tyr Pro Pro Gly Lys Glu Cys Asp
970 975 980

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Trp Arg Val Lys Val Asn Pro Asp Phe Val Ile Ala Leu Ile Phe Lys
985 990 995

agt ttc aac atg gag ccc agc tat gac ttc cta cac atc tat gaa 3375
Ser Phe Asn Met Glu Pro Ser Tyr Asp Phe Leu His Ile Tyr Glu
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Ile Met Asn Gly Thr Arg Val Gly Thr Asp Phe Lys Leu Gly Ser
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Thr Ile Thr Tyr Gln Cys Asp Ser Gly Tyr Lys Ile Leu Asp Pro
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Ser Ser Ile Thr Cys Val Ile Gly Ala Asp Gly Lys Pro Ser Trp
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1180 1185 1190

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Leu Leu Ser Ser Leu Ser Gly Ser His Ser Gly Glu Thr Leu Pro
1195 1200 1205

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Gly Ala Ser Ala Arg Gly Phe His Phe Val Tyr Gln Ala Val Pro
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Arg Thr Ser Asp Thr Gln Cys Ser Ser Val Pro Glu Pro Arg Tyr
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Gly Arg Arg Ile Gly Ser Glu Phe Ser Ala Gly Ser Ile Val Arg
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Phe Glu Xaa Asn Pro Gly Tyr Leu Leu Gln Gly Ser Thr Ala Leu
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His Cys Gln Ser Val Pro Asn Ala Leu Ala Gln Trp Asn Asp Thr
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Ile Pro Ser Cys Val Val Pro Cys Ser Gly Asn Phe Thr Gln Arg
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aga ggt aca atc ctg tcc ccc ggc tac cct gag cca tac gga aac      4320
Arg Gly Thr Ile Leu Ser Pro Gly Tyr Pro Glu Pro Tyr Gly Asn
1315                1320                1325

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Asn Leu Asn Cys Ile Trp Lys Ile Ile Val Thr Glu Gly Ser Gly
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Ile Gln Ile Gln Val Ile Ser Phe Ala Thr Glu Gln Asn Trp Asp
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tcc ctt gag atc cac gat ggt ggg gat gtg acc gca ccc aga ctg      4455
Ser Leu Glu Ile His Asp Gly Gly Asp Val Thr Ala Pro Arg Leu
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gga agc ttc tca ggc acc aca gta ccg gca ctg ctg aac agt act      4500
Gly Ser Phe Ser Gly Thr Thr Val Pro Ala Leu Leu Asn Ser Thr
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tcc aac caa ctc tac ctg cat ttc cag tct gac att agt gtg gca      4545
Ser Asn Gln Leu Tyr Leu His Phe Gln Ser Asp Ile Ser Val Ala
1390                1395                1400

gct gct ggt ttc cac ctg gaa tac aaa act gta ggt ctt gct gca      4590
Ala Ala Gly Phe His Leu Glu Tyr Lys Thr Val Gly Leu Ala Ala
1405                1410                1415

tgc caa gaa cca gcc ctc ccc agc aac agc atc aaa atc gga gat      4635
Cys Gln Glu Pro Ala Leu Pro Ser Asn Ser Ile Lys Ile Gly Asp
1420                1425                1430

cgg tac atg gtg aac gac gtg ctc tcc ttc cag tgc gag ccc ggg      4680
Arg Tyr Met Val Asn Asp Val Leu Ser Phe Gln Cys Glu Pro Gly
1435                1440                1445
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Tyr Thr Leu Gln Gly Arg Ser His Ile Ser Cys Met Pro Gly Thr
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Val Arg Arg Trp Asn Tyr Pro Ser Pro Leu Cys Ile Ala Thr Cys
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1495 1500 1505

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Ser Leu Pro Ile Gly Tyr Gly Ala His Ile Gln Phe Leu Asn Phe
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Ser Thr Glu Ala Asn His Asp Phe Leu Glu Ile Gln Asn Gly Pro
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1540 1545 1550

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Pro Ala Ala Leu Leu Ser Thr Thr His Glu Thr Leu Ile His Phe
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Tyr Ser Asp His Ser Gln Asn Arg Gln Gly Phe Lys Leu Ala Tyr
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Gln Ala Tyr Glu Leu Gln Asn Cys Pro Asp Pro Pro Pro Phe Gln
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1600 1605 1610

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Ser Phe Glu Cys Tyr Pro Gly Tyr Ile Leu Ile Gly His Pro Val
1615 1620 1625

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Leu Thr Cys Gln His Gly Ile Asn Arg Asn Trp Asn Tyr Pro Phe
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Pro Arg Cys Asp Ala Pro Cys Gly Tyr Asn Val Thr Ser Gln Asn
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Gly Thr Ile Tyr Ser Pro Gly Phe Pro Asp Glu Tyr Pro Ile Leu
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Lys Asp Cys Ile Trp Leu Ile Thr Val Pro Pro Gly His Gly Val
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Tyr Ile Asn Phe Thr Leu Leu Gln Thr Glu Ala Val Asn Asp Tyr
1690                1695                1700

att gct gtt tgg gac ggt ccc gat cag aac tca ccc cag ctg gga     5490
Ile Ala Val Trp Asp Gly Pro Asp Gln Asn Ser Pro Gln Leu Gly
1705                1710                1715

gtt ttc agt ggc aac aca gcc ctc gaa acg gcg tat agc tcc acc     5535
Val Phe Ser Gly Asn Thr Ala Leu Glu Thr Ala Tyr Ser Ser Thr
1720                1725                1730

aac caa gtc ctg ctc aag ttc cac agc gac ttt tca aat gga ggc     5580
Asn Gln Val Leu Leu Lys Phe His Ser Asp Phe Ser Asn Gly Gly
1735                1740                1745

ttc ttt gtc ctc aat ttc cac gca ttt cag ctc aag aaa tgt caa     5625
Phe Phe Val Leu Asn Phe His Ala Phe Gln Leu Lys Lys Cys Gln
1750                1755                1760

cct ccc cca gcg gtt cca cag gca gaa atg ctt act gag gat gat     5670
Pro Pro Pro Ala Val Pro Gln Ala Glu Met Leu Thr Glu Asp Asp
1765                1770                1775

gat ttc gag ata gga gat ttt gtg aag tac cag tgc cac ccc ggg     5715
Asp Phe Glu Ile Gly Asp Phe Val Lys Tyr Gln Cys His Pro Gly
1780                1785                1790

tac acc ttg gtg ggg acc gac att ctg act tgc aag ctc agt tcc     5760
Tyr Thr Leu Val Gly Thr Asp Ile Leu Thr Cys Lys Leu Ser Ser
1795                1800                1805

cag ttg cag ttt gag ggt tct ctc cca aca tgt gaa gca caa tgc     5805
Gln Leu Gln Phe Glu Gly Ser Leu Pro Thr Cys Glu Ala Gln Cys
1810                1815                1820

cca gca aat gaa gtc cgg act gga tca tcg gga gtc att ctc agt     5850
Pro Ala Asn Glu Val Arg Thr Gly Ser Ser Gly Val Ile Leu Ser
1825                1830                1835

cca ggg tat ccg ggt aat tat ttt aac tcc cag act tgc tct tgg     5895
Pro Gly Tyr Pro Gly Asn Tyr Phe Asn Ser Gln Thr Cys Ser Trp
1840                1845                1850

agt att aaa gtg gaa cca aac tac aac att acc atc ttt gtg gac     5940
Ser Ile Lys Val Glu Pro Asn Tyr Asn Ile Thr Ile Phe Val Asp
1855                1860                1865

aca ttt caa agt gaa aag cag ttt gat gca ctg gaa gtg ttt gat     5985
Thr Phe Gln Ser Glu Lys Gln Phe Asp Ala Leu Glu Val Phe Asp
1870                1875                1880

ggt tct tct ggg caa agt cct ctg cta gta gtc tta agt ggg aat     6030
Gly Ser Ser Gly Gln Ser Pro Leu Leu Val Val Leu Ser Gly Asn
1885                1890                1895

cat act gaa caa tca aat ttt aca agc agg agt aat cag tta tat     6075
His Thr Glu Gln Ser Asn Phe Thr Ser Arg Ser Asn Gln Leu Tyr
1900                1905                1910

ctc cgc tgg tcc act gac cat gcc acc agt aag aaa gga ttc aag     6120
Leu Arg Trp Ser Thr Asp His Ala Thr Ser Lys Lys Gly Phe Lys
1915                1920                1925
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att cgc tat gca gca cct tac tgc agt ttg acc cac ccc ctg aag 6165
Ile Arg Tyr Ala Ala Pro Tyr Cys Ser Leu Thr His Pro Leu Lys
1930                1935                1940

aat ggg ggt att cta aac agg act gca gga gcg gtt gga agc aaa 6210
Asn Gly Gly Ile Leu Asn Arg Thr Ala Gly Ala Val Gly Ser Lys
1945                1950                1955

gtg cat tat ttt tgc aag cct gga tac cga atg gtc ggc cac agc 6255
Val His Tyr Phe Cys Lys Pro Gly Tyr Arg Met Val Gly His Ser
1960                1965                1970

aat gca acc tgt aga cga aac cca ctt ggc atg tac cag tgg gac 6300
Asn Ala Thr Cys Arg Arg Asn Pro Leu Gly Met Tyr Gln Trp Asp
1975                1980                1985

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Ser Leu Thr Pro Leu Cys Gln Ala Val Ser Cys Gly Ile Pro Glu
1990                1995                2000

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Ser Pro Gly Asn Gly Ser Phe Thr Gly Asn Glu Phe Thr Leu Asp
2005                2010                2015

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Ser Lys Val Val Tyr Glu Cys His Glu Gly Phe Lys Leu Glu Ser
2020                2025                2030

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Ser Gln Gln Ala Thr Ala Val Cys Gln Glu Asp Gly Leu Trp Ser
2035                2040                2045

aac aag ggg aag ccg ccc acg tgt aag ccg gtc gct tgc ccc agc 6525
Asn Lys Gly Lys Pro Pro Thr Cys Lys Pro Val Ala Cys Pro Ser
2050                2055                2060

att gaa gct cag ctc tca gaa cat gtc atc tgg agg ctg gtt tca 6570
Ile Glu Ala Gln Leu Ser Glu His Val Ile Trp Arg Leu Val Ser
2065                2070                2075

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Gly Ser Leu Asn Glu Tyr Gly Ala Gln Val Leu Leu Ser Cys Ser
2080                2085                2090

cct ggt tac tac tta gaa ggc tgg agg ctc ctg cgg tgc cag gcc 6660
Pro Gly Tyr Tyr Leu Glu Gly Trp Arg Leu Leu Arg Cys Gln Ala
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Asn Gly Thr Trp Asn Ile Gly Asp Glu Arg Pro Ser Cys Arg Val
2110                2115                2120

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Ile Ser Cys Gly Ser Leu Ser Phe Pro Pro Asn Gly Asn Lys Ile
2125                2130                2135

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Gly Thr Leu Thr Val Tyr Gly Ala Thr Ala Ile Phe Thr Cys Asn
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Thr Gly Tyr Thr Leu Val Gly Ser His Val Arg Glu Cys Leu Ala
2155                2160                2165
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tgc ggt tcc cca gac ccg att gtg aac ggt cac att agt gga gat 6930
Cys Gly Ser Pro Asp Pro Ile Val Asn Gly His Ile Ser Gly Asp
2185 2190 2195

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Gly Phe Ser Tyr Arg Asp Thr Val Val Tyr Gln Cys Asn Pro Gly
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Phe Arg Leu Val Gly Thr Ser Val Arg Ile Cys Leu Gln Asp His
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Lys Trp Ser Gly Gln Thr Pro Val Cys Val Pro Ile Thr Cys Gly
2230 2235 2240

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His Pro Gly Asn Pro Ala His Gly Phe Thr Asn Gly Ser Glu Phe
2245 2250 2255

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Asn Leu Asn Asp Val Val Asn Phe Thr Cys Asn Thr Gly Tyr Leu
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Cys Gly Asp Pro Gly Thr Pro Ala His Gly Ser Arg Leu Gly Asp
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gac ttt aag aca aag agt ctt ctc cgc ttc tcc tgt gaa atg ggg 7695
Asp Phe Lys Thr Lys Ser Leu Leu Arg Phe Ser Cys Glu Met Gly
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Gly Asp Pro Gly Ile Pro Ala Tyr Gly Lys Arg Thr Gly Ser Ser Phe
        35                  40                  45

Leu His Gly Asp Thr Leu Thr Phe Glu Cys Pro Ala Ala Phe Glu Leu
    50                  55                  60

Val Gly Glu Arg Val Ile Thr Cys Gln Gln Asn Asn Gln Trp Ser Gly
65                  70                  75                  80

Asn Lys Pro Ser Cys Val Phe Ser Cys Phe Phe Asn Phe Thr Ala Ser
                85                  90                  95

Ser Gly Ile Ile Leu Ser Pro Asn Tyr Pro Glu Glu Tyr Gly Asn Asn
            100                 105                 110
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Met Asn Cys Val Trp Leu Ile Ile Ser Glu Pro Gly Ser Arg Ile His
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Val Lys Asp Asp Gly Ile Ser Asp Ile Thr Val Leu Gly Thr Phe Ser
145 150 155 160

Gly Asn Glu Val Pro Ser Gln Leu Ala Ser Ser Gly His Ile Val Arg
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Leu Glu Phe Gln Ser Asp His Ser Thr Thr Gly Arg Gly Phe Asn Ile
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Thr Tyr Thr Thr Phe Gly Gln Asn Glu Cys His Asp Pro Gly Ile Pro
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Ile Asn Gly Arg Arg Phe Gly Asp Arg Phe Leu Leu Gly Ser Ser Val
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Ser Phe His Cys Asp Asp Gly Phe Val Lys Thr Gln Gly Ser Glu Ser
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Val Ile Leu Pro Pro Gly Trp Pro Gly Tyr Tyr Lys Asp Ser Leu His
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Cys Glu Trp Ile Ile Glu Ala Lys Pro Gly His Ser Ile Lys Ile Thr
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305 310 315 320

Asp Gly Pro Ala Ser Ser Ser Pro Leu Ile Gly Glu Tyr His Gly Thr
325 330 335

Gln Ala Pro Gln Phe Leu Ile Ser Thr Gly Asn Phe Met Tyr Leu Leu
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Phe Thr Thr Asp Asn Ser Arg Ser Ser Ile Gly Phe Leu Ile His Tyr
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Glu Ser Val Thr Leu Glu Ser Asp Ser Cys Leu Asp Pro Gly Ile Pro
    370                 375                 380

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Thr Phe Ser Cys Asp Pro Gly Tyr Thr Leu Ser Asp Asp Glu Pro Leu
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Val Cys Glu Arg Asn His Gln Trp Asn His Ala Leu Pro Ser Cys Asp
            420                 425                 430

Ala Leu Cys Gly Gly Tyr Ile Gln Gly Lys Ser Gly Thr Val Leu Ser
        435                 440                 445

Pro Gly Phe Pro Asp Phe Tyr Pro Asn Ser Leu Asn Xaa Thr Trp Thr
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Ile Glu Val Ser His Gly Lys Gly Val Gln Met Ile Phe His Thr Phe
465                 470                 475                 480

His Leu Glu Ser Ser His Asp Tyr Leu Leu Ile Thr Glu Asp Gly Ser
                485                 490                 495

Phe Ser Glu Pro Val Ala Arg Leu Thr Gly Ser Val Leu Pro His Thr
            500                 505                 510

Ile Lys Ala Gly Leu Phe Gly Asn Phe Thr Ala Gln Leu Arg Phe Ile
        515                 520                 525

Ser Asp Phe Ser Ile Ser Tyr Glu Gly Phe Asn Ile Thr Phe Ser Glu
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Tyr Asp Leu Glu Pro Cys Asp Asp Pro Gly Val Pro Ala Phe Ser Arg
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Arg Ile Gly Phe His Phe Gly Val Gly Asp Ser Leu Thr Phe Ser Cys
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Cys Gly Ala Ser Val Lys Gly Asn Glu Gly Thr Leu Leu Ser Pro Asn
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660 665 670

Arg Pro Leu Gly Thr Phe Thr Lys Asn Glu Leu Leu Gly Leu Ile Leu
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Gln Gly Gln Ala Lys Ile Thr Cys Val Gln Leu Asn Asn Arg Phe Phe
930 935 940

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Tyr Phe Gln Thr Ala Leu Asn Asp Leu Ala Glu Leu Phe Asp Gly
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1190 1195 1200

Ser Gly Glu Thr Leu Pro Leu Ala Thr Ser Asn Gln Ile Leu Leu
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Pro Glu Pro Tyr Gly Asn Asn Leu Asn Cys Ile Trp Lys Ile Ile
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Val Thr Glu Gly Ser Gly Ile Gln Ile Gln Val Ile Ser Phe Ala
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Val Thr Ala Pro Arg Leu Gly Ser Phe Ser Gly Thr Thr Val Pro
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Ser Asp Ile Ser Val Ala Ala Ala Gly Phe His Leu Glu Tyr Lys
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Ser Ile Lys Ile Gly Asp Arg Tyr Met Val Asn Asp Val Leu Ser
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Ser Cys Met Pro Gly Thr Val Arg Arg Trp Asn Tyr Pro Ser Pro
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Leu Cys Ile Ala Thr Cys Gly Gly Thr Leu Ser Thr Leu Gly Gly
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Val Ile Leu Ser Pro Gly Phe Pro Gly Ser Tyr Pro Asn Asn Leu
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Glu Ile Gln Asn Gly Pro Tyr His Thr Ser Pro Met Ile Gly Gln
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Phe Ser Gly Thr Asp Leu Pro Ala Ala Leu Leu Ser Thr Thr His
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Glu Thr Leu Ile His Phe Tyr Ser Asp His Ser Gln Asn Arg Gln
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Gly Phe Lys Leu Ala Tyr Gln Ala Tyr Glu Leu Gln Asn Cys Pro
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Asp Pro Pro Pro Phe Gln Asn Gly Tyr Met Ile Asn Ser Asp Tyr
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Ser Val Gly Gln Ser Val Ser Phe Glu Cys Tyr Pro Gly Tyr Ile
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Asn Val Thr Ser Gln Asn Gly Thr Ile Tyr Ser Pro Gly Phe Pro
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Asp Glu Tyr Pro Ile Leu Lys Asp Cys Ile Trp Leu Ile Thr Val
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Pro Pro Gly His Gly Val Tyr Ile Asn Phe Thr Leu Leu Gln Thr
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Glu Ala Val Asn Asp Tyr Ile Ala Val Trp Asp Gly Pro Asp Gln
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Asn Ser Pro Gln Leu Gly Val Phe Ser Gly Asn Thr Ala Leu Glu
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Thr Ala Tyr Ser Ser Thr Asn Gln Val Leu Leu Lys Phe His Ser
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Asp Phe Ser Asn Gly Gly Phe Phe Val Leu Asn Phe His Ala Phe
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Gln Leu Lys Lys Cys Gln Pro Pro Pro Ala Val Pro Gln Ala Glu
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Met Leu Thr Glu Asp Asp Asp Phe Glu Ile Gly Asp Phe Val Lys
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Tyr Gln Cys His Pro Gly Tyr Thr Leu Val Gly Thr Asp Ile Leu
1790 1795 1800

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Ser Gly Val Ile Leu Ser Pro Gly Tyr Pro Gly Asn Tyr Phe Asn
1835 1840 1845

Ser Gln Thr Cys Ser Trp Ser Ile Lys Val Glu Pro Asn Tyr Asn
1850 1855 1860

Ile Thr Ile Phe Val Asp Thr Phe Gln Ser Glu Lys Gln Phe Asp
1865 1870 1875

Ala Leu Glu Val Phe Asp Gly Ser Ser Gly Gln Ser Pro Leu Leu
1880 1885 1890

Val Val Leu Ser Gly Asn His Thr Glu Gln Ser Asn Phe Thr Ser
1895 1900 1905

Arg Ser Asn Gln Leu Tyr Leu Arg Trp Ser Thr Asp His Ala Thr
1910 1915 1920

Ser Lys Lys Gly Phe Lys Ile Arg Tyr Ala Ala Pro Tyr Cys Ser
1925 1930 1935

Leu Thr His Pro Leu Lys Asn Gly Gly Ile Leu Asn Arg Thr Ala
1940 1945 1950

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1955 1960 1965

Arg Met Val Gly His Ser Asn Ala Thr Cys Arg Arg Asn Pro Leu
1970 1975 1980

Gly Met Tyr Gln Trp Asp Ser Leu Thr Pro Leu Cys Gln Ala Val
1985 1990 1995

Ser Cys Gly Ile Pro Glu Ser Pro Gly Asn Gly Ser Phe Thr Gly
2000 2005 2010

Asn Glu Phe Thr Leu Asp Ser Lys Val Val Tyr Glu Cys His Glu
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Gly Phe Lys Leu Glu Ser Ser Gln Gln Ala Thr Ala Val Cys Gln
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Glu Asp Gly Leu Trp Ser Asn Lys Gly Lys Pro Pro Thr Cys Lys
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Pro Val Ala Cys Pro Ser Ile Glu Ala Gln Leu Ser Glu His Val
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Cys Asn Thr Gly Tyr Leu Leu Gln Gly Val Ser Arg Ala Gln Cys
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Gly Gln Gln Asn Phe Pro Glu Ser Phe Glu Tyr Gly Met Ser Ile
2315 2320 2325

Leu Tyr His Cys Lys Lys Gly Phe Tyr Leu Leu Gly Ser Ser Ala
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Leu Thr Cys Met Ala Asn Gly Leu Trp Asp Arg Ser Leu Pro Lys
2345 2350 2355

Cys Leu Ala Ile Ser Cys Gly His Pro Gly Val Pro Ala Asn Ala
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Val Leu Thr Gly Glu Leu Phe Thr Tyr Gly Ala Val Val His Tyr
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Gly Asn Asn Pro Gly Phe Cys Gly Asp Pro Gly Thr Pro Ala His
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Gly Ser Arg Leu Gly Asp Asp Phe Lys Thr Lys Ser Leu Leu Arg
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Phe Ser Cys Glu Met Gly His Gln Leu Arg Gly Ser Pro Glu Arg
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Glu Ala Val Ser Cys Gly Asn Pro Gly Thr Pro Thr Asn Gly Met
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Ile Val Ser Ser Asp Gly Ile Leu Phe Ser Ser Ser Val Ile Tyr
2495 2500 2505

Ala Cys Trp Glu Gly Tyr Lys Thr Ser Gly Leu Met Thr Arg His
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Phe Gly Thr Asp Phe Thr Phe Asn Lys Thr Val Ser Tyr Gln Cys
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Glu Gly  Ser Asp Phe Arg Trp  Gly Ser Ser Ile Ser  Tyr Ser Cys
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Met Asp  Gly Tyr Gln Leu Ser  His Ser Ala Ile Leu  Ser Cys Glu
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Gly Arg  Gly Val Trp Lys Gly  Glu Ile Pro Gln Cys  Leu Pro Val
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Phe Cys  Gly Asp Pro Gly Ile  Pro Ala Glu Gly Arg  Leu Ser Gly
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Lys Ser  Phe Thr Tyr Lys Ser  Glu Val Phe Phe Gln  Cys Lys Ser
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Pro Phe  Ile Leu Val Gly Ser  Ser Arg Arg Val Cys  Gln Ala Asp
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Gly Thr  Trp Ser Gly Ile Gln  Pro Thr Cys Ile Asp  Pro Ala His
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Ser Ser  Arg Gly Tyr Glu Val  Gly Ser Thr Val Phe  Phe Arg Cys
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Arg Lys  Gly Tyr His Ile Gln  Gly Ser Thr Thr Arg  Thr Cys Leu
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Ala Asn  Leu Thr Trp Ser Gly  Ile Gln Thr Glu Cys  Ile Pro His
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Ala Cys  Arg Gln Pro Glu Thr  Pro Ala His Ala Asp  Val Arg Ala
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Ile Asp  Leu Pro Thr Phe Gly  Tyr Thr Leu Val Tyr  Thr Cys His
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Ser Asp Val Phe Phe Val Asn Ser Leu Trp Lys Gly Tyr Tyr Glu
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Tyr Leu Gly Lys Arg Gln Pro Ala Thr Leu Thr Val Asp Trp Phe
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Asn Ala Thr Ser Ser Lys Val Asn Ala Thr Phe Ser Glu Ala Ser
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Pro Val Glu Leu Lys Leu Thr Gly Ile Tyr Lys Lys Glu Glu Ala
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His Leu Leu Leu Lys Ala Phe Gln Ile Lys Gly Gln Ala Asp Ile
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Phe Val Ser Lys Phe Glu Asn Asp Asn Trp Gly Leu Asp Gly Tyr
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Val Ser Ser Gly Leu Glu Arg Gly Gly Phe Thr Phe Gln Gly Asp
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Ile His Gly Lys Asp Phe Gly Lys Phe Lys Leu Glu Arg Gln Asp
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Pro Leu Asn Pro Asp Gln Asp Ser Ser Ser His Tyr His Gly Thr
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Ser Ser Gly Ser Val Ala Ala Ala Ile Leu Val Pro Phe Phe Ala
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Leu Ile Leu Ser Gly Phe Ala Phe Tyr Leu Tyr Lys His Arg Thr
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Arg Pro Lys Val Gln Tyr Asn Gly Tyr Ala Gly His Glu Asn Ser
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Asn Gly Gln Ala Ser Phe Glu Asn Pro Met Tyr Asp Thr Asn Leu
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Gly Ser Ser Val Pro Asp Leu Ile Val Ser Met Ser Asn Gln Met Trp
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ctc cac ctg cag tca gac gac agc att ggt tcc cca gga ttt aaa gct 144
Leu His Leu Gln Ser Asp Asp Ser Ile Gly Ser Pro Gly Phe Lys Ala
35 40 45

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Val Tyr Gln Glu Ile Glu Lys Gly Gly Cys Gly Asp Pro Gly Ile Pro
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gcc tac ggg aag cgg act ggc agc agc ttc ttg cac ggg gac acg ctc 240
Ala Tyr Gly Lys Arg Thr Gly Ser Ser Phe Leu His Gly Asp Thr Leu
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acc ttt gag tgc cag gca gct ttt gag ctg gta gga gag aga gtg att 288
Thr Phe Glu Cys Gln Ala Ala Phe Glu Leu Val Gly Glu Arg Val Ile
85 90 95

acg tgc cag aga aac aac cag tgg tcc ggc aac aag cca agc tgt gtg 336
Thr Cys Gln Arg Asn Asn Gln Trp Ser Gly Asn Lys Pro Ser Cys Val
100 105 110

ttt tca tgt ttc ttc aac ttc acg gcg tcc tct ggg atc atc ctg tcg 384
Phe Ser Cys Phe Phe Asn Phe Thr Ala Ser Ser Gly Ile Ile Leu Ser
115 120 125

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cca aac tat cct gag gaa tat ggc aac aac atg aat tgt gtg tgg ttg      432
Pro Asn Tyr Pro Glu Glu Tyr Gly Asn Asn Met Asn Cys Val Trp Leu
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att ata tct gag ccc ggg agc cgg att cac ctc atc ttc aat gat ttc      480
Ile Ile Ser Glu Pro Gly Ser Arg Ile His Leu Ile Phe Asn Asp Phe
145                 150                 155                 160

gat gtg gag cct cag ttt gac ttc ctt gcg gtc aaa gat gat ggg att      528
Asp Val Glu Pro Gln Phe Asp Phe Leu Ala Val Lys Asp Asp Gly Ile
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tct gac atc aca gtc ctc ggg act ttc tct ggc aat gag gtg cct gca      576
Ser Asp Ile Thr Val Leu Gly Thr Phe Ser Gly Asn Glu Val Pro Ala
            180                 185                 190

cag ctg gcc ngc agt gga cac ata gta cgc ctg gag ttt cag tcc gat      624
Gln Leu Ala Xaa Ser Gly His Ile Val Arg Leu Glu Phe Gln Ser Asp
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cac tct acc acg ggc aga ggg ttc aac atc ata tac acc aca ttt ggt      672
His Ser Thr Thr Gly Arg Gly Phe Asn Ile Ile Tyr Thr Thr Phe Gly
    210                 215                 220

cag aac gag tgt cat gac cct ggg atc cct gtg aat gga cgg cgc ttt      720
Gln Asn Glu Cys His Asp Pro Gly Ile Pro Val Asn Gly Arg Arg Phe
225                 230                 235                 240

gga gac agg ttt ctg ctg gga agt tct gtg tcc ttc cac tgt gat gat      768
Gly Asp Arg Phe Leu Leu Gly Ser Ser Val Ser Phe His Cys Asp Asp
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ggc ttt gtg aag act cag ggt tct gag tct atc aca tgc atc ttg caa      816
Gly Phe Val Lys Thr Gln Gly Ser Glu Ser Ile Thr Cys Ile Leu Gln
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gat gga aac gtg gtc tgg agc tct act gtc cct cgc tgt gaa gct cct      864
Asp Gly Asn Val Val Trp Ser Ser Thr Val Pro Arg Cys Glu Ala Pro
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tgt ggt ggg cat ctg aca gct tct agt ggg gtc ata tta cct cca gga      912
Cys Gly Gly His Leu Thr Ala Ser Ser Gly Val Ile Leu Pro Pro Gly
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tgg cca gga tat tac aaa gat tct tta aat tgc gaa tgg gtc att gaa      960
Trp Pro Gly Tyr Tyr Lys Asp Ser Leu Asn Cys Glu Trp Val Ile Glu
305                 310                 315                 320

gcc aaa cca gga cat tcc atc aaa ata aca ttt gac agg ttc cag aca     1008
Ala Lys Pro Gly His Ser Ile Lys Ile Thr Phe Asp Arg Phe Gln Thr
                325                 330                 335

gaa gtc aat tat gat act ctg gaa gtc cgg gat ggg cca acc agc tca     1056
Glu Val Asn Tyr Asp Thr Leu Glu Val Arg Asp Gly Pro Thr Ser Ser
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tcc cca ctg att ggg gag tac cat ggc acc cag gct cca cag ttc ctc     1104
Ser Pro Leu Ile Gly Glu Tyr His Gly Thr Gln Ala Pro Gln Phe Leu
        355                 360                 365

atc agc aca ggg aac tac atg tac ctg ctg ttt acc act gac agc agc     1152
Ile Ser Thr Gly Asn Tyr Met Tyr Leu Leu Phe Thr Thr Asp Ser Ser
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Ser Asp Ser Cys Leu Asp Pro Gly Ile Pro Val Asn Gly His Arg His
405 410 415

ggc agt aac ttt ggt atc aga tct aca gtg acc ttc agc tgt gac cct 1296
Gly Ser Asn Phe Gly Ile Arg Ser Thr Val Thr Phe Ser Cys Asp Pro
420 425 430

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Gly Tyr Thr Leu Ser Asp Asp Asp Pro Leu Ile Cys Glu Lys Asn His
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Gln Trp Asn His Ala Leu Pro Ser Cys Asp Ala Leu Cys Gly Gly Tyr
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Ile His Gly Lys Ser Gly Thr Val Leu Ser Pro Gly Phe Pro Asp Phe
465 470 475 480

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Tyr Pro Asn Ser Leu Asn Cys Thr Trp Thr Ile Glu Val Ser His Gly
485 490 495

aag gga gtg cag atg aat ttc cac acc ttt cac ctt gaa agt tcc cac 1536
Lys Gly Val Gln Met Asn Phe His Thr Phe His Leu Glu Ser Ser His
500 505 510

gac tat ttg ctg atc aca gag gat ggg agt ttc tca gag ccg gta gcc 1584
Asp Tyr Leu Leu Ile Thr Glu Asp Gly Ser Phe Ser Glu Pro Val Ala
515 520 525

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Arg Leu Thr Gly Ser Val Leu Pro His Thr Ile Lys Ala Gly Leu Phe
530 535 540

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Gly Asn Phe Thr Ala Gln Leu Arg Phe Ile Ser Asp Phe Ser Ile Ser
545 550 555 560

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Tyr Glu Gly Phe Asn Ile Thr Phe Ala Glu Tyr Asp Leu Glu Pro Cys
565 570 575

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Asp Asp Pro Gly Val Pro Ala Tyr Ser Arg Arg Ile Gly Phe Gln Phe
580 585 590

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595 600 605

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Glu Gly Ala Thr Lys Leu Thr Cys Leu Gly Gly Gly Arg Arg Val Trp
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Ser Ala Pro Leu Pro Arg Cys Val Ala Glu Cys Gly Ala Ser Val Lys
625 630 635 640

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aat aac cat gag tgt atc tat aaa ata gaa aca gaa gcc gga aag ggg      2016
Asn Asn His Glu Cys Ile Tyr Lys Ile Glu Thr Glu Ala Gly Lys Gly
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atc cat ctc aga gcc cga acc ttc caa ctc ttc gaa gga gac act cta      2064
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aag gtt tat gat gga aag gac agc tcc tcg agg tca ctg gga gtc ttc      2112
Lys Val Tyr Asp Gly Lys Asp Ser Ser Ser Arg Ser Leu Gly Val Phe
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aca aga agt gaa ctg atg ggg ctg gtg cta aac agc acc tcc aac cac      2160
Thr Arg Ser Glu Leu Met Gly Leu Val Leu Asn Ser Thr Ser Asn His
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cag ctc acc tac acc agt ttt gac cta gtg aaa tgt gag gat cca ggc      2256
Gln Leu Thr Tyr Thr Ser Phe Asp Leu Val Lys Cys Glu Asp Pro Gly
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atc cct aac tat ggc tac agg atc cga gat gat ggt cac ttc aca gac      2304
Ile Pro Asn Tyr Gly Tyr Arg Ile Arg Asp Asp Gly His Phe Thr Asp
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act gtg gtt ctc tac agc tgc aac cca ggc tac gca atg cat ggc agc      2352
Thr Val Val Leu Tyr Ser Cys Asn Pro Gly Tyr Ala Met His Gly Ser
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agt acc ctg acc tgc ctg agt ggg gac cga agg gtg tgg gac aaa cct      2400
Ser Thr Leu Thr Cys Leu Ser Gly Asp Arg Arg Val Trp Asp Lys Pro
785                 790                 795                 800

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Met Pro Ser Cys Val Ala Glu Cys Gly Gly Leu Val His Ala Ala Thr
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Ser Gly Arg Ile Leu Ser Pro Gly Tyr Pro Ala Pro Tyr Asp Asn Asn
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Leu His Cys Thr Trp Thr Ile Glu Ala Asp Pro Gly Lys Thr Xaa Ser
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ctc cat ttc att gtg ttt gac act gaa acg gcg cac gac atc ctc aag      2592
Leu His Phe Ile Val Phe Asp Thr Glu Thr Ala His Asp Ile Leu Lys
    850                 855                 860

gtc tgg gat ggt cca gtg gac agc aac atc ctg ctg aag gag tgg agc      2640
Val Trp Asp Gly Pro Val Asp Ser Asn Ile Leu Leu Lys Glu Trp Ser
865                 870                 875                 880

ggc tcg gcc ctt cct gag gac atc cac agc acc ttc aac tcg ctc acc      2688
Gly Ser Ala Leu Pro Glu Asp Ile His Ser Thr Phe Asn Ser Leu Thr
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cag ttc tct act tcc att gca tcc acc tgc aat gac cct ggg atg cct      2784
Gln Phe Ser Thr Ser Ile Ala Ser Thr Cys Asn Asp Pro Gly Met Pro
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cag aat gga acc cgc tat ggt gac agc cgg gaa cct gga gac acc atc      2832
Gln Asn Gly Thr Arg Tyr Gly Asp Ser Arg Glu Pro Gly Asp Thr Ile
    930                 935                 940

acc ttc cag tgt gac cct gga tac cag ctc caa ggg caa gcc aag atc      2880
Thr Phe Gln Cys Asp Pro Gly Tyr Gln Leu Gln Gly Gln Ala Lys Ile
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Thr Cys Val Gln Leu Asn Asn Arg Phe Phe Trp Gln Pro Asp Pro Pro
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Ser Cys Ile Ala Ala Cys Gly Gly Asn Leu Thr Gly Pro Ala Gly Val
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Ile Leu Ser Pro Asn Tyr Pro Gln  Pro Tyr Pro Pro Gly  Lys Glu Cys
        995                 1000                1005

gac tgg  aga att aag gtg aac  cca gac ttt gtc att  gcc tta ata      3069
Asp Trp  Arg Ile Lys Val Asn  Pro Asp Phe Val Ile  Ala Leu Ile
    1010                 1015                 1020

ttc aaa  agt ttt agc atg gag  cca agt tac gac ttc  ctg cat atc      3114
Phe Lys  Ser Phe Ser Met Glu  Pro Ser Tyr Asp Phe  Leu His Ile
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tat gaa  ggg aag gac tcc aac  agc cca ctg atc gga  agc ttc cag      3159
Tyr Glu  Gly Lys Asp Ser Asn  Ser Pro Leu Ile Gly  Ser Phe Gln
    1040                 1045                 1050

ggt tct  caa gcc cca gag agg  att gag agc agt ggt  aac agc ctc      3204
Gly Ser  Gln Ala Pro Glu Arg  Ile Glu Ser Ser Gly  Asn Ser Leu
    1055                 1060                 1065

ttc ctg  gca ttc agg agt gat  gcc tct gtt ggc ctg  tcc ggg ttt      3249
Phe Leu  Ala Phe Arg Ser Asp  Ala Ser Val Gly Leu  Ser Gly Phe
    1070                 1075                 1080

gcc att  gaa ttt aaa gag aaa  cca cgg gaa gct tgc  ttt gac cct      3294
Ala Ile  Glu Phe Lys Glu Lys  Pro Arg Glu Ala Cys  Phe Asp Pro
    1085                 1090                 1095

ggg aac  ata atg aac ggg aca  agg att gga acg gac  ttt aag ctg      3339
Gly Asn  Ile Met Asn Gly Thr  Arg Ile Gly Thr Asp  Phe Lys Leu
    1100                 1105                 1110

ggc tct  aca gtt acc tat caa  tgt gac tct ggt tac  aag att gtg      3384
Gly Ser  Thr Val Thr Tyr Gln  Cys Asp Ser Gly Tyr  Lys Ile Val
    1115                 1120                 1125

gat ccc  tca tcc att gag tgt  gtg aca ggg gct gat  ggg aag ccg      3429
Asp Pro  Ser Ser Ile Glu Cys  Val Thr Gly Ala Asp  Gly Lys Pro
    1130                 1135                 1140
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tcc tgg gac cgg gca ctg cct gcc tgc caa gca ccc tgt gga ggc   3474
Ser Trp Asp Arg Ala Leu Pro Ala Cys Gln Ala Pro Cys Gly Gly
    1145                1150                1155

caa tac atg ggc tcg gag ggg gta gtt ttg tca cca aac tac cct   3519
Gln Tyr Met Gly Ser Glu Gly Val Val Leu Ser Pro Asn Tyr Pro
    1160                1165                1170

cat aac tac acg gct ggg cag ata tgc atc tat tcc atc acg gtg   3564
His Asn Tyr Thr Ala Gly Gln Ile Cys Ile Tyr Ser Ile Thr Val
    1175                1180                1185

ccc aag gaa ttt gtg gtg ttt gga cag ttt gcc tat ttc cag act   3609
Pro Lys Glu Phe Val Val Phe Gly Gln Phe Ala Tyr Phe Gln Thr
    1190                1195                1200

gcg ctg aac gac ttg gca gaa ttg ttt gat gga acc cat cct cag   3654
Ala Leu Asn Asp Leu Ala Glu Leu Phe Asp Gly Thr His Pro Gln
    1205                1210                1215

gcc agg ctt ctc agt tct ctc tct ggt tcc cat tca ggt gaa aca   3699
Ala Arg Leu Leu Ser Ser Leu Ser Gly Ser His Ser Gly Glu Thr
    1220                1225                1230

ctc ccg ctg gct aca tcc aat cag att ctg ctt cgc ttc agc gca   3744
Leu Pro Leu Ala Thr Ser Asn Gln Ile Leu Leu Arg Phe Ser Ala
    1235                1240                1245

aag agc gga gct tct gca cgg ggt ttc cac ttc gtc tac caa gcc   3789
Lys Ser Gly Ala Ser Ala Arg Gly Phe His Phe Val Tyr Gln Ala
    1250                1255                1260

gtc cca cgc acc agt gac acg cag tgc agc tcc gtc cct gag ccc   3834
Val Pro Arg Thr Ser Asp Thr Gln Cys Ser Ser Val Pro Glu Pro
    1265                1270                1275

aga tat ggg aga agg att ggt tct gag ttc tct gca ggc tcc atc   3879
Arg Tyr Gly Arg Arg Ile Gly Ser Glu Phe Ser Ala Gly Ser Ile
    1280                1285                1290

gtc cga ttc gag tgc aac cca ggt tac ctg ctg caa ggc tcc aca   3924
Val Arg Phe Glu Cys Asn Pro Gly Tyr Leu Leu Gln Gly Ser Thr
    1295                1300                1305

gcc atc cgt tgt cag tct gtg cca aac gct ttg gcc cag tgg aat   3969
Ala Ile Arg Cys Gln Ser Val Pro Asn Ala Leu Ala Gln Trp Asn
    1310                1315                1320

gac acc atc cca agc tgt gta gtt cca tgc agt ggc aat ttc act   4014
Asp Thr Ile Pro Ser Cys Val Val Pro Cys Ser Gly Asn Phe Thr
    1325                1330                1335

cag aga aga ggg aca atc tta tct cca ggc tac cct gag ccc tat   4059
Gln Arg Arg Gly Thr Ile Leu Ser Pro Gly Tyr Pro Glu Pro Tyr
    1340                1345                1350

ggg aac aac ctg aac tgt gta tgg aag atc ata gta tcg gag ggc   4104
Gly Asn Asn Leu Asn Cys Val Trp Lys Ile Ile Val Ser Glu Gly
    1355                1360                1365

tca ggg atc cag atc caa gtg att agc ttt gcc acg gag cag aac   4149
Ser Gly Ile Gln Ile Gln Val Ile Ser Phe Ala Thr Glu Gln Asn
    1370                1375                1380
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tgg gac  tcc ctg gag atc cat  gac gga gga gac atg  acg gcc ccc        4194
Trp Asp  Ser Leu Glu Ile His  Asp Gly Gly Asp Met  Thr Ala Pro
    1385                 1390                 1395

aga ctg  ggc agc ttc tca ggt  acc aca gtg ccc gca  ctg ctg aat        4239
Arg Leu  Gly Ser Phe Ser Gly  Thr Thr Val Pro Ala  Leu Leu Asn
    1400                 1405                 1410

agc acc  tcc aac cag ctc tgc  ctg cac ttc cag tcg  gac atc agt        4284
Ser Thr  Ser Asn Gln Leu Cys  Leu His Phe Gln Ser  Asp Ile Ser
    1415                 1420                 1425

gtt gcc  gct gcg ggc ttt cac  ctg gaa tac aaa acg  gtg ggt ctg        4329
Val Ala  Ala Ala Gly Phe His  Leu Glu Tyr Lys Thr  Val Gly Leu
    1430                 1435                 1440

gct gcg  tgc cag gaa cct gct  ctc ccg agc aac ggc  atc aag ata        4374
Ala Ala  Cys Gln Glu Pro Ala  Leu Pro Ser Asn Gly  Ile Lys Ile
    1445                 1450                 1455

gga gac  cgc tat atg gtg aac  gat gtg ctg tcc ttc  cag tgc gag        4419
Gly Asp  Arg Tyr Met Val Asn  Asp Val Leu Ser Phe  Gln Cys Glu
    1460                 1465                 1470

cct ggg  tac acc ttg cag ggc  cgc tca cac att tct  tgt atg ccg        4464
Pro Gly  Tyr Thr Leu Gln Gly  Arg Ser His Ile Ser  Cys Met Pro
    1475                 1480                 1485

gga act  gta cgt cgc tgg aac  tat cct tcc cct ctg  tgc att gcc        4509
Gly Thr  Val Arg Arg Trp Asn  Tyr Pro Ser Pro Leu  Cys Ile Ala
    1490                 1495                 1500

acc tgt  ggt ggg aca ctg acc  agc atg agt gga gtg  atc ctg agc        4554
Thr Cys  Gly Gly Thr Leu Thr  Ser Met Ser Gly Val  Ile Leu Ser
    1505                 1510                 1515

cca ggc  ttc cca ggg tca tac  ccc aac aac ctg gac  tgc acc tgg        4599
Pro Gly  Phe Pro Gly Ser Tyr  Pro Asn Asn Leu Asp  Cys Thr Trp
    1520                 1525                 1530

aag ata  tcc ctg ccc att ggc  tat ggt gca cat atc  caa ttt ctg        4644
Lys Ile  Ser Leu Pro Ile Gly  Tyr Gly Ala His Ile  Gln Phe Leu
    1535                 1540                 1545

aat ttc  tca act gaa gcc aac  cat gac tac ctg gag  atc cag aat        4689
Asn Phe  Ser Thr Glu Ala Asn  His Asp Tyr Leu Glu  Ile Gln Asn
    1550                 1555                 1560

ggc cct  tac cac agt agt cca  atg atg gga cag ttc  agt ggc cct        4734
Gly Pro  Tyr His Ser Ser Pro  Met Met Gly Gln Phe  Ser Gly Pro
    1565                 1570                 1575

gac ctg  cct gcg tca ctg ctg  agc acc aca cat gaa  acc ctc atc        4779
Asp Leu  Pro Ala Ser Leu Leu  Ser Thr Thr His Glu  Thr Leu Ile
    1580                 1585                 1590

cgc ttc  tat agt gac cac tca  cag aac cga caa gga  ttt aaa ctc        4824
Arg Phe  Tyr Ser Asp His Ser  Gln Asn Arg Gln Gly  Phe Lys Leu
    1595                 1600                 1605

agt tac  caa gct tat gag tta  cag aac tgc ccg gac  cca ccc gca        4869
Ser Tyr  Gln Ala Tyr Glu Leu  Gln Asn Cys Pro Asp  Pro Pro Ala
    1610                 1615                 1620
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ttc cag aat ggg ttc atg atc aac tcc gat tac agc gtg ggc cag        4914
Phe Gln Asn Gly Phe Met Ile Asn Ser Asp Tyr Ser Val Gly Gln
    1625                1630                1635

tcg atc tca ttt gag tgc tac ccg ggc tac atc ttg cta ggc cac        4959
Ser Ile Ser Phe Glu Cys Tyr Pro Gly Tyr Ile Leu Leu Gly His
    1640                1645                1650

cct gtg ctc acc tgc cag cat ggc act gac agg aac tgg aac tac        5004
Pro Val Leu Thr Cys Gln His Gly Thr Asp Arg Asn Trp Asn Tyr
    1655                1660                1665

cct ttc cca cgg tgt gac gct ccc tgt ggg tat aat gtg aca tca        5049
Pro Phe Pro Arg Cys Asp Ala Pro Cys Gly Tyr Asn Val Thr Ser
    1670                1675                1680

cag aat ggc acc att tat tcc cct ggg ttc cca gac gag tat cca        5094
Gln Asn Gly Thr Ile Tyr Ser Pro Gly Phe Pro Asp Glu Tyr Pro
    1685                1690                1695

att ctg aag gac tgc ctg tgg ctg gtc act gtc cct cca gga cat        5139
Ile Leu Lys Asp Cys Leu Trp Leu Val Thr Val Pro Pro Gly His
    1700                1705                1710

gga gtg tac atc aac ttc acc ttg ctg cag act gag gct gta aat        5184
Gly Val Tyr Ile Asn Phe Thr Leu Leu Gln Thr Glu Ala Val Asn
    1715                1720                1725

gac tac atc gct gtg tgg gat ggt cct gac cag aac tcg cct cag        5229
Asp Tyr Ile Ala Val Trp Asp Gly Pro Asp Gln Asn Ser Pro Gln
    1730                1735                1740

ctc ggg gtc ttc agt gga aac act gcc ctc gag aca gca tac agc        5274
Leu Gly Val Phe Ser Gly Asn Thr Ala Leu Glu Thr Ala Tyr Ser
    1745                1750                1755

tcc acc aac cag gtc ttg ctc aaa ttc cac agc gat ttc tcc aat        5319
Ser Thr Asn Gln Val Leu Leu Lys Phe His Ser Asp Phe Ser Asn
    1760                1765                1770

gga ggc ttc ttt gtc ctc aat ttt cat gca ttt caa ctg aag agg        5364
Gly Gly Phe Phe Val Leu Asn Phe His Ala Phe Gln Leu Lys Arg
    1775                1780                1785

tgc ccg cct cct cca gta gtg ccg cag gct gac ctg ctt aca gaa        5409
Cys Pro Pro Pro Pro Val Val Pro Gln Ala Asp Leu Leu Thr Glu
    1790                1795                1800

gat gaa gac ttt gaa ata ggg gac ttc gta aag tac cag tgc cat        5454
Asp Glu Asp Phe Glu Ile Gly Asp Phe Val Lys Tyr Gln Cys His
    1805                1810                1815

cca ggg tac acg ctg ttg gga agt gac acc ctg aca tgc aag ctc        5499
Pro Gly Tyr Thr Leu Leu Gly Ser Asp Thr Leu Thr Cys Lys Leu
    1820                1825                1830

agc tca cag cta ttg ttc caa ggc tct cca cct acc tgt gaa gca        5544
Ser Ser Gln Leu Leu Phe Gln Gly Ser Pro Pro Thr Cys Glu Ala
    1835                1840                1845

caa tgc cca gcc aat gaa gtg cga aca gag tct tct ggg gtg att        5589
Gln Cys Pro Ala Asn Glu Val Arg Thr Glu Ser Ser Gly Val Ile
    1850                1855                1860
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ctc agt cct ggg tac cca ggc aac tat ttt aac tcc cag aca tgt 5634
Leu Ser Pro Gly Tyr Pro Gly Asn Tyr Phe Asn Ser Gln Thr Cys
1865 1870 1875

gct tgg agt att aaa gtg gag cca aac ttt aac att acg ctc ttt 5679
Ala Trp Ser Ile Lys Val Glu Pro Asn Phe Asn Ile Thr Leu Phe
1880 1885 1890

gtg gac acc ttt caa agt gaa aag caa ttt gat gca ctg gaa gta 5724
Val Asp Thr Phe Gln Ser Glu Lys Gln Phe Asp Ala Leu Glu Val
1895 1900 1905

ttt gat ggt tct tct ggg caa agt cct ttg tta gtg gtc tta agt 5769
Phe Asp Gly Ser Ser Gly Gln Ser Pro Leu Leu Val Val Leu Ser
1910 1915 1920

ggg aac cac act gaa cag tcc aat ttt acc agc aga agt aac cat 5814
Gly Asn His Thr Glu Gln Ser Asn Phe Thr Ser Arg Ser Asn His
1925 1930 1935

ctg tac ctc cgc tgg tcc aca gat cat gca acc agc aag aaa gga 5859
Leu Tyr Leu Arg Trp Ser Thr Asp His Ala Thr Ser Lys Lys Gly
1940 1945 1950

ttc aag att cgc tat gca gct cct tac tgc agc ctc acc tct aca 5904
Phe Lys Ile Arg Tyr Ala Ala Pro Tyr Cys Ser Leu Thr Ser Thr
1955 1960 1965

ctc aag aat ggt ggc gtt tta aat aaa acc gca ggc gcc ctg ggg 5949
Leu Lys Asn Gly Gly Val Leu Asn Lys Thr Ala Gly Ala Leu Gly
1970 1975 1980

agc aag gtg cag tat ttc tgc aag cct gga tat cga atg att ggc 5994
Ser Lys Val Gln Tyr Phe Cys Lys Pro Gly Tyr Arg Met Ile Gly
1985 1990 1995

cac agc aac gcc acc tgc agg cgg aac cca gtg ggc gtg tac cag 6039
His Ser Asn Ala Thr Cys Arg Arg Asn Pro Val Gly Val Tyr Gln
2000 2005 2010

tgg gac tcg atg gca ccg ctt tgc cag gct gtg tcc tgt gga att 6084
Trp Asp Ser Met Ala Pro Leu Cys Gln Ala Val Ser Cys Gly Ile
2015 2020 2025

cca gag gct cca gga aat ggc tcg ttc aca ggc aat gag ttc acc 6129
Pro Glu Ala Pro Gly Asn Gly Ser Phe Thr Gly Asn Glu Phe Thr
2030 2035 2040

tta gac agt aaa gtg act tat gaa tgt aat gaa ggc ttc aag ctg 6174
Leu Asp Ser Lys Val Thr Tyr Glu Cys Asn Glu Gly Phe Lys Leu
2045 2050 2055

gat gcc agt cag caa gcc act gct gtg tgt caa gaa gat ggc ctg 6219
Asp Ala Ser Gln Gln Ala Thr Ala Val Cys Gln Glu Asp Gly Leu
2060 2065 2070

tgg agc aac aga gga aag cca ccc acg tgc aaa ccg gtg ccc tgc 6264
Trp Ser Asn Arg Gly Lys Pro Pro Thr Cys Lys Pro Val Pro Cys
2075 2080 2085

ccc agc atc gaa ggc cag ctg tca gag cac gtg ctc tgg agg ctg 6309
Pro Ser Ile Glu Gly Gln Leu Ser Glu His Val Leu Trp Arg Leu
2090 2095 2100

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gtt tcg  gga tca ttg aat gaa  tat gga gct caa gtt  ctc ctc agc      6354
Val Ser  Gly Ser Leu Asn Glu  Tyr Gly Ala Gln Val  Leu Leu Ser
    2105                2110                 2115

tgt agt  cct ggc tac ttc ttg  cag ggt cag agg ctg  ttg cag tgc      6399
Cys Ser  Pro Gly Tyr Phe Leu  Gln Gly Gln Arg Leu  Leu Gln Cys
    2120                2125                 2130

caa gcc  aat ggg acc tgg aac  act gag gag gac aga  ccc aga tgt      6444
Gln Ala  Asn Gly Thr Trp Asn  Thr Glu Glu Asp Arg  Pro Arg Cys
    2135                2140                 2145

aaa gtc  atc tcc tgt gga agc  ctg tcc ttt ccc cca  aat ggt aac      6489
Lys Val  Ile Ser Cys Gly Ser  Leu Ser Phe Pro Pro  Asn Gly Asn
    2150                2155                 2160

aag ata  ggg acg ctc act atg  tat gga gcc acc gcc  atc ttt acc      6534
Lys Ile  Gly Thr Leu Thr Met  Tyr Gly Ala Thr Ala  Ile Phe Thr
    2165                2170                 2175

tgc aat  acc ggc tac aca ctt  gta ggc tcc cat gtc  cgg gag tgc      6579
Cys Asn  Thr Gly Tyr Thr Leu  Val Gly Ser His Val  Arg Glu Cys
    2180                2185                 2190

ttg gcc  aat ggt ctc tgg agc  gga tct gaa aca agg  tgc ctg gcg      6624
Leu Ala  Asn Gly Leu Trp Ser  Gly Ser Glu Thr Arg  Cys Leu Ala
    2195                2200                 2205

ggt cat  tgt ggc tct cca gac  ccc att gtg aat ggc  cat atc agt      6669
Gly His  Cys Gly Ser Pro Asp  Pro Ile Val Asn Gly  His Ile Ser
    2210                2215                 2220

ggc gat  ggc ttc agc tac agg  gac aca gtg gtc tac  caa tgc aac      6714
Gly Asp  Gly Phe Ser Tyr Arg  Asp Thr Val Val Tyr  Gln Cys Asn
    2225                2230                 2235

cct ggg  ttt cga ctc gta ggc  acg tct gtg agg att  tgc ctg cag      6759
Pro Gly  Phe Arg Leu Val Gly  Thr Ser Val Arg Ile  Cys Leu Gln
    2240                2245                 2250

gac cac  aag tgg tcg ggg cag  acc ccc gtt tgc gtc  ccc atc aca      6804
Asp His  Lys Trp Ser Gly Gln  Thr Pro Val Cys Val  Pro Ile Thr
    2255                2260                 2265

tgt gga  cac cct gga aac cct  gcc cat ggc ctc acc  aac ggc agc      6849
Cys Gly  His Pro Gly Asn Pro  Ala His Gly Leu Thr  Asn Gly Ser
    2270                2275                 2280

gag ttc  aac ctg aat gac ctt  gtg aat ttc acc tgc  cat acg ggc      6894
Glu Phe  Asn Leu Asn Asp Leu  Val Asn Phe Thr Cys  His Thr Gly
    2285                2290                 2295

tac ctg  ctg cag ggt gcc tcc  cga gcc caa tgt cgg  agc aac ggc      6939
Tyr Leu  Leu Gln Gly Ala Ser  Arg Ala Gln Cys Arg  Ser Asn Gly
    2300                2305                 2310

cag tgg  agc agc ccc ttg cct  atc tgc cga gtg gtg  aac tgt tcc      6984
Gln Trp  Ser Ser Pro Leu Pro  Ile Cys Arg Val Val  Asn Cys Ser
    2315                2320                 2325

gat cct  gga ttt gtg gaa aat  gca gtt cgc cac ggg  caa cag aac      7029
Asp Pro  Gly Phe Val Glu Asn  Ala Val Arg His Gly  Gln Gln Asn
    2330                2335                 2340
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ttt cca gag agt ttc gag tat ggg aca agt gtg atg tat cac tgc 7074
Phe Pro Glu Ser Phe Glu Tyr Gly Thr Ser Val Met Tyr His Cys
    2345                2350                2355

aag aag ggg ttc tac cta ctg ggc tct tct gcc ctg acc tgc atg 7119
Lys Lys Gly Phe Tyr Leu Leu Gly Ser Ser Ala Leu Thr Cys Met
    2360                2365                2370

gca agt ggc ttg tgg gac cgc tcc tta ccc aag tgt ctg gct ata 7164
Ala Ser Gly Leu Trp Asp Arg Ser Leu Pro Lys Cys Leu Ala Ile
    2375                2380                2385

tca tgt ggg cat cct ggg gtc ccc gct aat gct gtc ctg act gga 7209
Ser Cys Gly His Pro Gly Val Pro Ala Asn Ala Val Leu Thr Gly
    2390                2395                2400

gaa ttg ttt aca ttt gga gcc aca gtt cag tac tcc tgc aaa ggg 7254
Glu Leu Phe Thr Phe Gly Ala Thr Val Gln Tyr Ser Cys Lys Gly
    2405                2410                2415

ggc cag att ctc aca ggc aat agc aca aga gtc tgc caa gaa gac 7299
Gly Gln Ile Leu Thr Gly Asn Ser Thr Arg Val Cys Gln Glu Asp
    2420                2425                2430

agt cac tgg agt gga tcc ctt ccc cat tgt tca gga aat agt cct 7344
Ser His Trp Ser Gly Ser Leu Pro His Cys Ser Gly Asn Ser Pro
    2435                2440                2445

gga ttt tgt ggt gat cca ggg acc cca gca cat ggg tct cgt ctt 7389
Gly Phe Cys Gly Asp Pro Gly Thr Pro Ala His Gly Ser Arg Leu
    2450                2455                2460

ggg gat gag ttt aag aca aag agt ctt ttg cga ttc tcc tgt gag 7434
Gly Asp Glu Phe Lys Thr Lys Ser Leu Leu Arg Phe Ser Cys Glu
    2465                2470                2475

atg ggc cac cag ctg cgg ggt tct gca gag cgc aca tgc ctg gtg 7479
Met Gly His Gln Leu Arg Gly Ser Ala Glu Arg Thr Cys Leu Val
    2480                2485                2490

aat ggg tcc tgg tca gga gtc cag cct gtg tgt gag gcc gtg tcc 7524
Asn Gly Ser Trp Ser Gly Val Gln Pro Val Cys Glu Ala Val Ser
    2495                2500                2505

tgt gga aac cct ggc acc cct acc aat ggg atg atc ctc agc agc 7569
Cys Gly Asn Pro Gly Thr Pro Thr Asn Gly Met Ile Leu Ser Ser
    2510                2515                2520

gat gga atc ctc ttc tcc agc tct gtc atc tat gcc tgc tgg gaa 7614
Asp Gly Ile Leu Phe Ser Ser Ser Val Ile Tyr Ala Cys Trp Glu
    2525                2530                2535

ggc tac aag acc tcg ggg ctc atg acg cgg cac tgc aca gcg aac 7659
Gly Tyr Lys Thr Ser Gly Leu Met Thr Arg His Cys Thr Ala Asn
    2540                2545                2550

ggg aca tgg aca ggc aca gcc cct gac tgt aca atc atc agc tgt 7704
Gly Thr Trp Thr Gly Thr Ala Pro Asp Cys Thr Ile Ile Ser Cys
    2555                2560                2565

ggt gat cct ggc aca ctg ccc aat ggc atc cag ttt ggg aca gac 7749
Gly Asp Pro Gly Thr Leu Pro Asn Gly Ile Gln Phe Gly Thr Asp
    2570                2575                2580
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ttc act  ttc aac aag acc gtg  agc tat cag tgc aac  cct ggc tac      7794
Phe Thr  Phe Asn Lys Thr Val  Ser Tyr Gln Cys Asn  Pro Gly Tyr
    2585                 2590                 2595

ctg atg  gag ccc cca aca tca  ccc acc atc cgc tgc  acc aaa gat      7839
Leu Met  Glu Pro Pro Thr Ser  Pro Thr Ile Arg Cys  Thr Lys Asp
    2600                 2605                 2610

ggt aca  tgg aat cag acc cgg  ccc ctc tgc aaa gct  gtt cta tgc      7884
Gly Thr  Trp Asn Gln Thr Arg  Pro Leu Cys Lys Ala  Val Leu Cys
    2615                 2620                 2625

agc cag  cct ccc tca gtg cca  aac gga aag gtg gag  ggg tca gac      7929
Ser Gln  Pro Pro Ser Val Pro  Asn Gly Lys Val Glu  Gly Ser Asp
    2630                 2635                 2640

ttc cga  tgg ggt gcc agc ata  agc tac agt tgt gtg  gat ggc tac      7974
Phe Arg  Trp Gly Ala Ser Ile  Ser Tyr Ser Cys Val  Asp Gly Tyr
    2645                 2650                 2655

cag ctc  tcc cac tcg gcc atc  ctg tcc tgt gaa ggg  cgt gga gta      8019
Gln Leu  Ser His Ser Ala Ile  Leu Ser Cys Glu Gly  Arg Gly Val
    2660                 2665                 2670

tgg aaa  gga gaa gtc cct cag  tgc ttg cct gtg ttc  tgt ggc gat      8064
Trp Lys  Gly Glu Val Pro Gln  Cys Leu Pro Val Phe  Cys Gly Asp
    2675                 2680                 2685

cca ggc  act cca gca gag gga  cgg ctc agt ggg aaa  agc ttc acc      8109
Pro Gly  Thr Pro Ala Glu Gly  Arg Leu Ser Gly Lys  Ser Phe Thr
    2690                 2695                 2700

ttt aag  tct gag gtc ttc atc  cag tgc aaa ccc cca  ttt gtg tta      8154
Phe Lys  Ser Glu Val Phe Ile  Gln Cys Lys Pro Pro  Phe Val Leu
    2705                 2710                 2715

gtg ggt  tcc tcg agg aga acc  tgc cag gcc gat ggg  atg tgg agt      8199
Val Gly  Ser Ser Arg Arg Thr  Cys Gln Ala Asp Gly  Met Trp Ser
    2720                 2725                 2730

ggc atc  cag ccc act tgt ata  gat cca gcc cac acc  gct tgc cca      8244
Gly Ile  Gln Pro Thr Cys Ile  Asp Pro Ala His Thr  Ala Cys Pro
    2735                 2740                 2745

gac ccc  ggc act ccc cac ttt  gga ata cag aat agc  tcg aaa gga      8289
Asp Pro  Gly Thr Pro His Phe  Gly Ile Gln Asn Ser  Ser Lys Gly
    2750                 2755                 2760

tac gag  gtt gga agc act gtg  ttc ttc aga tgt aga  aaa ggt tac      8334
Tyr Glu  Val Gly Ser Thr Val  Phe Phe Arg Cys Arg  Lys Gly Tyr
    2765                 2770                 2775

cac atc  caa ggc tcc act acc  cgg acc tgt ctt gcc  aac ctc acg      8379
His Ile  Gln Gly Ser Thr Thr  Arg Thr Cys Leu Ala  Asn Leu Thr
    2780                 2785                 2790

tgg agt  gga atc cag aca gag  tgc atc ccc cat gcc  tgc cgg cag      8424
Trp Ser  Gly Ile Gln Thr Glu  Cys Ile Pro His Ala  Cys Arg Gln
    2795                 2800                 2805

cca gag  acc cca gcg cat gca  gat gtg aga gcc atc  gat ctt cca      8469
Pro Glu  Thr Pro Ala His Ala  Asp Val Arg Ala Ile  Asp Leu Pro
    2810                 2815                 2820
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gct ttt ggc tac acc tta gtc tac acc tgt cat cca gga ttt ttc     8514
Ala Phe Gly Tyr Thr Leu Val Tyr Thr Cys His Pro Gly Phe Phe
    2825                2830                2835

ctt gct ggc gga tct gag cac agg acg tgt aaa gca gac atg aaa     8559
Leu Ala Gly Gly Ser Glu His Arg Thr Cys Lys Ala Asp Met Lys
    2840                2845                2850

tgg aca gga aag tca cct gtt tgt aaa agt aaa gga gtg aga gaa     8604
Trp Thr Gly Lys Ser Pro Val Cys Lys Ser Lys Gly Val Arg Glu
    2855                2860                2865

gtt aat gaa aca gtt act aaa act cca gtt cct tct gat gta ttt     8649
Val Asn Glu Thr Val Thr Lys Thr Pro Val Pro Ser Asp Val Phe
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ttc atc aac tcg gtg tgg aag gga tat tat gaa tat tta ggc aag     8694
Phe Ile Asn Ser Val Trp Lys Gly Tyr Tyr Glu Tyr Leu Gly Lys
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aga cag ccg gcg act ctc act gtg gac tgg ttt aat gca acc agc     8739
Arg Gln Pro Ala Thr Leu Thr Val Asp Trp Phe Asn Ala Thr Ser
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agc aag gtc aat gcg acc ttc acc gca gcc tca cag gtg cag ctg     8784
Ser Lys Val Asn Ala Thr Phe Thr Ala Ala Ser Gln Val Gln Leu
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gag ctg aca ggg gtc tac aag aag gaa gag gcc cac ctg ctt ctg     8829
Glu Leu Thr Gly Val Tyr Lys Lys Glu Glu Ala His Leu Leu Leu
    2930                2935                2940

aaa gcc ttt cat atc aaa ggc cca gca gat att ttt gta agc aag     8874
Lys Ala Phe His Ile Lys Gly Pro Ala Asp Ile Phe Val Ser Lys
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ttt gaa aat gac aac tgg gga ctc gat ggt tat gta tcc tca gga     8919
Phe Glu Asn Asp Asn Trp Gly Leu Asp Gly Tyr Val Ser Ser Gly
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ctt gag aga gga gga ttc tcc ttt cag ggt gat ata cat gga aaa     8964
Leu Glu Arg Gly Gly Phe Ser Phe Gln Gly Asp Ile His Gly Lys
    2975                2980                2985

gac ttc ggg aag ttc aag ctg gaa aga caa gat cct tcc aac tct     9009
Asp Phe Gly Lys Phe Lys Leu Glu Arg Gln Asp Pro Ser Asn Ser
    2990                2995                3000

gat gca gat tct tca aat cat tac cag ggc acc agc agt ggc tct     9054
Asp Ala Asp Ser Ser Asn His Tyr Gln Gly Thr Ser Ser Gly Ser
    3005                3010                3015

gtg gca gct gcg att ctc gtc ccc ttc ttc gct cta att cta tca     9099
Val Ala Ala Ala Ile Leu Val Pro Phe Phe Ala Leu Ile Leu Ser
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ggg ttt gca ttt tac ctc tac aaa cac aga aca aga cca aaa gtt     9144
Gly Phe Ala Phe Tyr Leu Tyr Lys His Arg Thr Arg Pro Lys Val
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caa tac aat ggc tat gct ggc cat gaa aac agt aat gga caa gct     9189
Gln Tyr Asn Gly Tyr Ala Gly His Glu Asn Ser Asn Gly Gln Ala
    3050                3055                3060
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tca ttt  gaa aac ccc atg tat  gat aca aac tta aaa  ccc aca gag       9234
Ser Phe  Glu Asn Pro Met Tyr  Asp Thr Asn Leu Lys  Pro Thr Glu
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gcc aag  gct gtg agg ttt gac  acg act ctg aac aca  gtg tgt aca       9279
Ala Lys  Ala Val Arg Phe Asp  Thr Thr Leu Asn Thr  Val Cys Thr
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gtg gta  tagccctcag tgccccctag gaccgactca tagccatacc tctgatggac      9335
Val Val
    3095

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<212> PRT

<213> Rattus rattus

<400> 4

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            20                  25                  30

Leu His Leu Gln Ser Asp Asp Ser Ile Gly Ser Pro Gly Phe Lys Ala
        35                  40                  45

Val Tyr Gln Glu Ile Glu Lys Gly Gly Cys Gly Asp Pro Gly Ile Pro
    50                  55                  60

Ala Tyr Gly Lys Arg Thr Gly Ser Ser Phe Leu His Gly Asp Thr Leu
65                  70                  75                  80

Thr Phe Glu Cys Gln Ala Ala Phe Glu Leu Val Gly Glu Arg Val Ile
                85                  90                  95

Thr Cys Gln Arg Asn Asn Gln Trp Ser Gly Asn Lys Pro Ser Cys Val
            100                 105                 110

Phe Ser Cys Phe Phe Asn Phe Thr Ala Ser Ser Gly Ile Ile Leu Ser
        115                 120                 125

Pro Asn Tyr Pro Glu Glu Tyr Gly Asn Asn Met Asn Cys Val Trp Leu
    130                 135                 140

Ile Ile Ser Glu Pro Gly Ser Arg Ile His Leu Ile Phe Asn Asp Phe
145                 150                 155                 160

Asp Val Glu Pro Gln Phe Asp Phe Leu Ala Val Lys Asp Asp Gly Ile
                165                 170                 175

Ser Asp Ile Thr Val Leu Gly Thr Phe Ser Gly Asn Glu Val Pro Ala
            180                 185                 190

Gln Leu Ala Xaa Ser Gly His Ile Val Arg Leu Glu Phe Gln Ser Asp
        195                 200                 205

His Ser Thr Thr Gly Arg Gly Phe Asn Ile Ile Tyr Thr Thr Phe Gly
    210                 215                 220
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Gln Asn Glu Cys His Asp Pro Gly Ile Pro Val Asn Gly Arg Arg Phe
225 230 235 240

Gly Asp Arg Phe Leu Leu Gly Ser Ser Val Ser Phe His Cys Asp Asp
245 250 255

Gly Phe Val Lys Thr Gln Gly Ser Glu Ser Ile Thr Cys Ile Leu Gln
260 265 270

Asp Gly Asn Val Val Trp Ser Ser Thr Val Pro Arg Cys Glu Ala Pro
275 280 285

Cys Gly Gly His Leu Thr Ala Ser Ser Gly Val Ile Leu Pro Pro Gly
290 295 300

Trp Pro Gly Tyr Tyr Lys Asp Ser Leu Asn Cys Glu Trp Val Ile Glu
305 310 315 320

Ala Lys Pro Gly His Ser Ile Lys Ile Thr Phe Asp Arg Phe Gln Thr
325 330 335

Glu Val Asn Tyr Asp Thr Leu Glu Val Arg Asp Gly Pro Thr Ser Ser
340 345 350

Ser Pro Leu Ile Gly Glu Tyr His Gly Thr Gln Ala Pro Gln Phe Leu
355 360 365

Ile Ser Thr Gly Asn Tyr Met Tyr Leu Leu Phe Thr Thr Asp Ser Ser
370 375 380

Arg Ala Ser Val Gly Phe Leu Ile His Tyr Glu Ser Val Thr Leu Glu
385 390 395 400

Ser Asp Ser Cys Leu Asp Pro Gly Ile Pro Val Asn Gly His Arg His
405 410 415

Gly Ser Asn Phe Gly Ile Arg Ser Thr Val Thr Phe Ser Cys Asp Pro
420 425 430

Gly Tyr Thr Leu Ser Asp Asp Asp Pro Leu Ile Cys Glu Lys Asn His
435 440 445

Gln Trp Asn His Ala Leu Pro Ser Cys Asp Ala Leu Cys Gly Gly Tyr
450 455 460

Ile His Gly Lys Ser Gly Thr Val Leu Ser Pro Gly Phe Pro Asp Phe
465 470 475 480

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Tyr Pro Asn Ser Leu Asn Cys Thr Trp Thr Ile Glu Val Ser His Gly
                485                 490                 495

Lys Gly Val Gln Met Asn Phe His Thr Phe His Leu Glu Ser Ser His
            500                 505                 510

Asp Tyr Leu Leu Ile Thr Glu Asp Gly Ser Phe Ser Glu Pro Val Ala
        515                 520                 525

Arg Leu Thr Gly Ser Val Leu Pro His Thr Ile Lys Ala Gly Leu Phe
    530                 535                 540

Gly Asn Phe Thr Ala Gln Leu Arg Phe Ile Ser Asp Phe Ser Ile Ser
545                 550                 555                 560

Tyr Glu Gly Phe Asn Ile Thr Phe Ala Glu Tyr Asp Leu Glu Pro Cys
                565                 570                 575

Asp Asp Pro Gly Val Pro Ala Tyr Ser Arg Arg Ile Gly Phe Gln Phe
            580                 585                 590

Gly Val Gly Asp Thr Leu Ala Phe Thr Cys Phe Gln Gly Tyr Arg Leu
        595                 600                 605

Glu Gly Ala Thr Lys Leu Thr Cys Leu Gly Gly Gly Arg Arg Val Trp
    610                 615                 620

Ser Ala Pro Leu Pro Arg Cys Val Ala Glu Cys Gly Ala Ser Val Lys
625                 630                 635                 640

Gly Asn Glu Gly Thr Leu Leu Ser Pro Asn Phe Pro Ser Asn Tyr Asp
                645                 650                 655

Asn Asn His Glu Cys Ile Tyr Lys Ile Glu Thr Glu Ala Gly Lys Gly
            660                 665                 670

Ile His Leu Arg Ala Arg Thr Phe Gln Leu Phe Glu Gly Asp Thr Leu
        675                 680                 685

Lys Val Tyr Asp Gly Lys Asp Ser Ser Ser Arg Ser Leu Gly Val Phe
    690                 695                 700

Thr Arg Ser Glu Leu Met Gly Leu Val Leu Asn Ser Thr Ser Asn His
705                 710                 715                 720

Leu Arg Leu Glu Phe Asn Ser Asn Gly Ser Asp Thr Ala Gln Gly Phe
                725                 730                 735
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Gln Leu Thr Tyr Thr Ser Phe Asp Leu Val Lys Cys Glu Asp Pro Gly
            740                 745                 750

Ile Pro Asn Tyr Gly Tyr Arg Ile Arg Asp Asp Gly His Phe Thr Asp
        755                 760                 765

Thr Val Val Leu Tyr Ser Cys Asn Pro Gly Tyr Ala Met His Gly Ser
    770                 775                 780

Ser Thr Leu Thr Cys Leu Ser Gly Asp Arg Arg Val Trp Asp Lys Pro
785                 790                 795                 800

Met Pro Ser Cys Val Ala Glu Cys Gly Gly Leu Val His Ala Ala Thr
                805                 810                 815

Ser Gly Arg Ile Leu Ser Pro Gly Tyr Pro Ala Pro Tyr Asp Asn Asn
            820                 825                 830

Leu His Cys Thr Trp Thr Ile Glu Ala Asp Pro Gly Lys Thr Xaa Ser
        835                 840                 845

Leu His Phe Ile Val Phe Asp Thr Glu Thr Ala His Asp Ile Leu Lys
    850                 855                 860

Val Trp Asp Gly Pro Val Asp Ser Asn Ile Leu Leu Lys Glu Trp Ser
865                 870                 875                 880

Gly Ser Ala Leu Pro Glu Asp Ile His Ser Thr Phe Asn Ser Leu Thr
                885                 890                 895

Leu Gln Phe Asp Ser Asp Phe Phe Ile Ser Lys Ser Gly Phe Ser Ile
            900                 905                 910

Gln Phe Ser Thr Ser Ile Ala Ser Thr Cys Asn Asp Pro Gly Met Pro
        915                 920                 925

Gln Asn Gly Thr Arg Tyr Gly Asp Ser Arg Glu Pro Gly Asp Thr Ile
    930                 935                 940

Thr Phe Gln Cys Asp Pro Gly Tyr Gln Leu Gln Gly Gln Ala Lys Ile
945                 950                 955                 960

Thr Cys Val Gln Leu Asn Asn Arg Phe Phe Trp Gln Pro Asp Pro Pro
                965                 970                 975

Ser Cys Ile Ala Ala Cys Gly Gly Asn Leu Thr Gly Pro Ala Gly Val
            980                 985                 990
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Ile Leu Ser Pro Asn Tyr Pro Gln  Pro Tyr Pro Pro Gly  Lys Glu Cys
            995                     1000                   1005

Asp Trp  Arg Ile Lys Val Asn  Pro Asp Phe Val Ile  Ala Leu Ile
    1010                 1015                 1020

Phe Lys  Ser Phe Ser Met Glu  Pro Ser Tyr Asp Phe  Leu His Ile
    1025                 1030                 1035

Tyr Glu  Gly Lys Asp Ser Asn  Ser Pro Leu Ile Gly  Ser Phe Gln
    1040                 1045                 1050

Gly Ser  Gln Ala Pro Glu Arg  Ile Glu Ser Ser Gly  Asn Ser Leu
    1055                 1060                 1065

Phe Leu  Ala Phe Arg Ser Asp  Ala Ser Val Gly Leu  Ser Gly Phe
    1070                 1075                 1080

Ala Ile  Glu Phe Lys Glu Lys  Pro Arg Glu Ala Cys  Phe Asp Pro
    1085                 1090                 1095

Gly Asn  Ile Met Asn Gly Thr  Arg Ile Gly Thr Asp  Phe Lys Leu
    1100                 1105                 1110

Gly Ser  Thr Val Thr Tyr Gln  Cys Asp Ser Gly Tyr  Lys Ile Val
    1115                 1120                 1125

Asp Pro  Ser Ser Ile Glu Cys  Val Thr Gly Ala Asp  Gly Lys Pro
    1130                 1135                 1140

Ser Trp  Asp Arg Ala Leu Pro  Ala Cys Gln Ala Pro  Cys Gly Gly
    1145                 1150                 1155

Gln Tyr  Met Gly Ser Glu Gly  Val Val Leu Ser Pro  Asn Tyr Pro
    1160                 1165                 1170

His Asn  Tyr Thr Ala Gly Gln  Ile Cys Ile Tyr Ser  Ile Thr Val
    1175                 1180                 1185

Pro Lys  Glu Phe Val Val Phe  Gly Gln Phe Ala Tyr  Phe Gln Thr
    1190                 1195                 1200

Ala Leu  Asn Asp Leu Ala Glu  Leu Phe Asp Gly Thr  His Pro Gln
    1205                 1210                 1215

Ala Arg  Leu Leu Ser Ser Leu  Ser Gly Ser His Ser  Gly Glu Thr
    1220                 1225                 1230
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Leu Pro Leu Ala Thr Ser Asn Gln Ile Leu Leu Arg Phe Ser Ala
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Lys Ser Gly Ala Ser Ala Arg Gly Phe His Phe Val Tyr Gln Ala
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Val Pro Arg Thr Ser Asp Thr Gln Cys Ser Ser Val Pro Glu Pro
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Arg Tyr Gly Arg Arg Ile Gly Ser Glu Phe Ser Ala Gly Ser Ile
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Val Arg Phe Glu Cys Asn Pro Gly Tyr Leu Leu Gln Gly Ser Thr
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Ala Ile Arg Cys Gln Ser Val Pro Asn Ala Leu Ala Gln Trp Asn
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Asp Thr Ile Pro Ser Cys Val Val Pro Cys Ser Gly Asn Phe Thr
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Gln Arg Arg Gly Thr Ile Leu Ser Pro Gly Tyr Pro Glu Pro Tyr
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Gly Asn Asn Leu Asn Cys Val Trp Lys Ile Ile Val Ser Glu Gly
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Ser Gly Ile Gln Ile Gln Val Ile Ser Phe Ala Thr Glu Gln Asn
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Trp Asp Ser Leu Glu Ile His Asp Gly Gly Asp Met Thr Ala Pro
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Arg Leu Gly Ser Phe Ser Gly Thr Thr Val Pro Ala Leu Leu Asn
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Ser Thr Ser Asn Gln Leu Cys Leu His Phe Gln Ser Asp Ile Ser
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Val Ala Ala Ala Gly Phe His Leu Glu Tyr Lys Thr Val Gly Leu
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Ala Ala Cys Gln Glu Pro Ala Leu Pro Ser Asn Gly Ile Lys Ile
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Gly Asp Arg Tyr Met Val Asn Asp Val Leu Ser Phe Gln Cys Glu
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Pro Gly Tyr Thr Leu Gln Gly Arg Ser His Ile Ser Cys Met Pro
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Gly Thr Val Arg Arg Trp Asn Tyr Pro Ser Pro Leu Cys Ile Ala
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Thr Cys Gly Gly Thr Leu Thr Ser Met Ser Gly Val Ile Leu Ser
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Pro Gly Phe Pro Gly Ser Tyr Pro Asn Asn Leu Asp Cys Thr Trp
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Lys Ile Ser Leu Pro Ile Gly Tyr Gly Ala His Ile Gln Phe Leu
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Asn Phe Ser Thr Glu Ala Asn His Asp Tyr Leu Glu Ile Gln Asn
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Gly Pro Tyr His Ser Ser Pro Met Met Gly Gln Phe Ser Gly Pro
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Asp Leu Pro Ala Ser Leu Leu Ser Thr Thr His Glu Thr Leu Ile
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Arg Phe Tyr Ser Asp His Ser Gln Asn Arg Gln Gly Phe Lys Leu
1595 1600 1605

Ser Tyr Gln Ala Tyr Glu Leu Gln Asn Cys Pro Asp Pro Pro Ala
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Phe Gln Asn Gly Phe Met Ile Asn Ser Asp Tyr Ser Val Gly Gln
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Ser Ile Ser Phe Glu Cys Tyr Pro Gly Tyr Ile Leu Leu Gly His
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Pro Val Leu Thr Cys Gln His Gly Thr Asp Arg Asn Trp Asn Tyr
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Pro Phe Pro Arg Cys Asp Ala Pro Cys Gly Tyr Asn Val Thr Ser
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Gln Asn Gly Thr Ile Tyr Ser Pro Gly Phe Pro Asp Glu Tyr Pro
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Ile Leu Lys Asp Cys Leu Trp Leu Val Thr Val Pro Pro Gly His
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Gly Val Tyr Ile Asn Phe Thr Leu Leu Gln Thr Glu Ala Val Asn
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Asp Tyr Ile Ala Val Trp Asp Gly Pro Asp Gln Asn Ser Pro Gln
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Leu Gly Val Phe Ser Gly Asn Thr Ala Leu Glu Thr Ala Tyr Ser
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Ser Thr Asn Gln Val Leu Leu Lys Phe His Ser Asp Phe Ser Asn
1760 1765 1770

Gly Gly Phe Phe Val Leu Asn Phe His Ala Phe Gln Leu Lys Arg
1775 1780 1785

Cys Pro Pro Pro Pro Val Val Pro Gln Ala Asp Leu Leu Thr Glu
1790 1795 1800

Asp Glu Asp Phe Glu Ile Gly Asp Phe Val Lys Tyr Gln Cys His
1805 1810 1815

Pro Gly Tyr Thr Leu Leu Gly Ser Asp Thr Leu Thr Cys Lys Leu
1820 1825 1830

Ser Ser Gln Leu Leu Phe Gln Gly Ser Pro Pro Thr Cys Glu Ala
1835 1840 1845

Gln Cys Pro Ala Asn Glu Val Arg Thr Glu Ser Ser Gly Val Ile
1850 1855 1860

Leu Ser Pro Gly Tyr Pro Gly Asn Tyr Phe Asn Ser Gln Thr Cys
1865 1870 1875

Ala Trp Ser Ile Lys Val Glu Pro Asn Phe Asn Ile Thr Leu Phe
1880 1885 1890

Val Asp Thr Phe Gln Ser Glu Lys Gln Phe Asp Ala Leu Glu Val
1895 1900 1905

Phe Asp Gly Ser Ser Gly Gln Ser Pro Leu Leu Val Val Leu Ser
1910 1915 1920

Gly Asn His Thr Glu Gln Ser Asn Phe Thr Ser Arg Ser Asn His
1925 1930 1935

Leu Tyr Leu Arg Trp Ser Thr Asp His Ala Thr Ser Lys Lys Gly
1940 1945 1950

Phe Lys Ile Arg Tyr Ala Ala Pro Tyr Cys Ser Leu Thr Ser Thr
1955 1960 1965

Leu Lys Asn Gly Gly Val Leu Asn Lys Thr Ala Gly Ala Leu Gly
1970 1975 1980

Ser Lys Val Gln Tyr Phe Cys Lys Pro Gly Tyr Arg Met Ile Gly
1985 1990 1995

His Ser Asn Ala Thr Cys Arg Arg Asn Pro Val Gly Val Tyr Gln
2000 2005 2010

Trp Asp Ser Met Ala Pro Leu Cys Gln Ala Val Ser Cys Gly Ile
2015 2020 2025

Pro Glu Ala Pro Gly Asn Gly Ser Phe Thr Gly Asn Glu Phe Thr
2030 2035 2040

Leu Asp Ser Lys Val Thr Tyr Glu Cys Asn Glu Gly Phe Lys Leu
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Asp Ala Ser Gln Gln Ala Thr Ala Val Cys Gln Glu Asp Gly Leu
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Trp Ser Asn Arg Gly Lys Pro Pro Thr Cys Lys Pro Val Pro Cys
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Pro Ser Ile Glu Gly Gln Leu Ser Glu His Val Leu Trp Arg Leu
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Val Ser Gly Ser Leu Asn Glu Tyr Gly Ala Gln Val Leu Leu Ser
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Cys Ser Pro Gly Tyr Phe Leu Gln Gly Gln Arg Leu Leu Gln Cys
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Lys Val Ile Ser Cys Gly Ser Leu Ser Phe Pro Pro Asn Gly Asn
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Cys Asn Thr Gly Tyr Thr Leu Val Gly Ser His Val Arg Glu Cys
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Leu Ala Asn Gly Leu Trp Ser Gly Ser Glu Thr Arg Cys Leu Ala
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Gly His Cys Gly Ser Pro Asp Pro Ile Val Asn Gly His Ile Ser
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Pro Gly Phe Arg Leu Val Gly Thr Ser Val Arg Ile Cys Leu Gln
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Asp His Lys Trp Ser Gly Gln Thr Pro Val Cys Val Pro Ile Thr
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Cys Gly His Pro Gly Asn Pro Ala His Gly Leu Thr Asn Gly Ser
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Glu Phe Asn Leu Asn Asp Leu Val Asn Phe Thr Cys His Thr Gly
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Tyr Leu Leu Gln Gly Ala Ser Arg Ala Gln Cys Arg Ser Asn Gly
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Asp Pro Gly Phe Val Glu Asn Ala Val Arg His Gly Gln Gln Asn
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Lys Lys Gly Phe Tyr Leu Leu Gly Ser Ser Ala Leu Thr Cys Met
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Met Gly His Gln Leu Arg Gly Ser Ala Glu Arg Thr Cys Leu Val
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Asn Gly Ser Trp Ser Gly Val Gln Pro Val Cys Glu Ala Val Ser
2495 2500 2505

Cys Gly Asn Pro Gly Thr Pro Thr Asn Gly Met Ile Leu Ser Ser
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Asp Gly Ile Leu Phe Ser Ser Ser Val Ile Tyr Ala Cys Trp Glu
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Gly Tyr Lys Thr Ser Gly Leu Met Thr Arg His Cys Thr Ala Asn
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Gly Asp Pro Gly Thr Leu Pro Asn Gly Ile Gln Phe Gly Thr Asp
2570 2575 2580

Phe Thr Phe Asn Lys Thr Val Ser Tyr Gln Cys Asn Pro Gly Tyr
2585 2590 2595

Leu Met Glu Pro Pro Thr Ser Pro Thr Ile Arg Cys Thr Lys Asp
2600 2605 2610

Gly Thr Trp Asn Gln Thr Arg Pro Leu Cys Lys Ala Val Leu Cys
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Ser Gln Pro Pro Ser Val Pro Asn Gly Lys Val Glu Gly Ser Asp
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Phe Arg Trp Gly Ala Ser Ile Ser Tyr Ser Cys Val Asp Gly Tyr
2645 2650 2655

Gln Leu Ser His Ser Ala Ile Leu Ser Cys Glu Gly Arg Gly Val
2660 2665 2670

Trp Lys Gly Glu Val Pro Gln Cys Leu Pro Val Phe Cys Gly Asp
2675 2680 2685

Pro Gly Thr Pro Ala Glu Gly Arg Leu Ser Gly Lys Ser Phe Thr
2690 2695 2700

Phe Lys Ser Glu Val Phe Ile Gln Cys Lys Pro Pro Phe Val Leu
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Val Gly Ser Ser Arg Arg Thr Cys Gln Ala Asp Gly Met Trp Ser
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Gly Ile Gln Pro Thr Cys Ile Asp Pro Ala His Thr Ala Cys Pro
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Asp Pro Gly Thr Pro His Phe Gly Ile Gln Asn Ser Ser Lys Gly
2750 2755 2760

Tyr Glu Val Gly Ser Thr Val Phe Phe Arg Cys Arg Lys Gly Tyr
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His Ile Gln Gly Ser Thr Thr Arg Thr Cys Leu Ala Asn Leu Thr
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Trp Ser Gly Ile Gln Thr Glu Cys Ile Pro His Ala Cys Arg Gln
2795 2800 2805

Pro Glu Thr Pro Ala His Ala Asp Val Arg Ala Ile Asp Leu Pro
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Ala Phe Gly Tyr Thr Leu Val Tyr Thr Cys His Pro Gly Phe Phe
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Leu Ala Gly Gly Ser Glu His Arg Thr Cys Lys Ala Asp Met Lys
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Trp Thr Gly Lys Ser Pro Val Cys Lys Ser Lys Gly Val Arg Glu
2855 2860 2865

Val Asn Glu Thr Val Thr Lys Thr Pro Val Pro Ser Asp Val Phe
2870 2875 2880

Phe Ile Asn Ser Val Trp Lys Gly Tyr Tyr Glu Tyr Leu Gly Lys
2885 2890 2895

Arg Gln Pro Ala Thr Leu Thr Val Asp Trp Phe Asn Ala Thr Ser
2900 2905 2910

Ser Lys Val Asn Ala Thr Phe Thr Ala Ala Ser Gln Val Gln Leu
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Glu Leu Thr Gly Val Tyr Lys Lys Glu Glu Ala His Leu Leu Leu
2930 2935 2940

Lys Ala Phe His Ile Lys Gly Pro Ala Asp Ile Phe Val Ser Lys
2945 2950 2955

Phe Glu Asn Asp Asn Trp Gly Leu Asp Gly Tyr Val Ser Ser Gly
2960 2965 2970

Leu Glu Arg Gly Gly Phe Ser Phe Gln Gly Asp Ile His Gly Lys
2975 2980 2985

Asp Phe Gly Lys Phe Lys Leu Glu Arg Gln Asp Pro Ser Asn Ser
2990 2995 3000

Asp Ala Asp Ser Ser Asn His Tyr Gln Gly Thr Ser Ser Gly Ser
3005 3010 3015

Val Ala Ala Ala Ile Leu Val Pro Phe Phe Ala Leu Ile Leu Ser
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Gly Phe Ala Phe Tyr Leu Tyr Lys His Arg Thr Arg Pro Lys Val
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Gln Tyr Asn Gly Tyr Ala Gly His Glu Asn Ser Asn Gly Gln Ala
3050 3055 3060

Ser Phe Glu Asn Pro Met Tyr Asp Thr Asn Leu Lys Pro Thr Glu
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Val Val
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35 40 45

Asp Thr Gln Asn Cys Pro Asp Pro Pro Pro Phe Gln Asn Gly Tyr Met
50 55 60

Ile Asn Ser Asp Tyr Ser Val Gly Gln Ser Val Ser Phe Glu Cys Tyr
65 70 75 80

Pro Gly Tyr Ile Leu Ile Gly His Pro Val Leu Thr Cys Gln His Gly
85 90 95

Ile Asn Val Ile Trp Asp Asn Glu Thr Pro Ile Cys Asp Arg Ile Pro
100 105 110

Cys Gly Leu Pro Pro Thr Ile Thr Asn Gly Asp Phe Ile Ser Thr Asn
115 120 125

Arg Glu Asn Phe His Tyr Gly Ser Val Val Thr Tyr Arg Cys Asn Pro
130 135 140

Gly Arg Asn Trp Asn Tyr Pro Phe Pro Arg Cys Asp Ala Pro Cys Gly
145 150 155 160

Tyr Asn Val Thr Ser Gln Asn Gly Thr Ile Tyr Ser Pro Gly Phe Pro
165 170 175

Asp Glu Tyr Pro Ile Leu Lys Asp Cys Ile Trp Leu Ile Thr Val Pro
180 185 190

Pro Gly Ser Gly Gly Arg Lys Val Phe Glu Leu Val Gly Glu Pro Ser
195 200 205

Ile Tyr Cys Thr Ser Asn Asp Asp Gln Val Gly Ile Trp Ser Gly Pro
210 215 220

Ala Pro Gln Cys Ile Ile Pro Asn Lys Cys Thr Pro Pro Asn Val Glu
225 230 235 240

Asn His Gly Val Tyr Ile Asn Phe Thr Leu Leu Gln Thr Glu Ala Val
245 250 255

Asn Asp Tyr Ile Ala Val Trp Asp Gly Pro Asp Gln Asn Ser Pro Gln
260 265 270

Leu Gly Val Phe Ser Gly Asn Thr Ala Leu Glu Thr Gly Ile Leu Val
275 280 285

Ser Asp Asn Arg Ser Leu Phe Ser Leu Asn Glu Val Val Glu Phe Arg
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Cys Gln Pro Gly Phe Val Met Lys Gly Pro Arg Arg Val Lys Cys Gln
305 310 315 320

Ala Leu Asn Lys Trp Glu Pro Glu Leu Pro Ser Cys Ser Arg Ala Tyr
325 330 335

Ser Ser Thr Asn Gln Val Leu Leu Lys Phe His Ser Asp Phe Ser Asn
340 345 350

Gly Gly Phe Phe Val Leu Asn Phe His Ala Phe Gln Leu Lys Val Cys
355 360 365

Gln Pro Pro Pro Asp Val Leu His Ala Glu Arg Thr Gln Arg Asp Lys
370 375 380

Asp Asn Phe Ser Pro Gly Gln Glu Val Phe Tyr Ser Cys Glu Pro Gly
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Tyr Asp Leu Arg Gly Ala Ala Ser Met Arg Cys Thr Pro Gln Lys Cys
405 410 415

Gln Pro Pro Pro Ala Val Pro Gln Ala Glu Met Leu Thr Glu Asp Asp
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Asp Phe Glu Ile Gly Asp Phe Val Lys Tyr Gln Cys His Pro Gly Tyr
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Thr Leu Val Gly Thr Asp Ile Leu Thr Cys Lys Leu Ser Ser Gln Gly
450 455 460

Asp Trp Ser Pro Ala Ala Pro Thr Cys Glu Val Lys Ser Cys Asp Asp
465 470 475 480

Phe Met Gly Gln Leu Leu Asn Gly Arg Leu Gln Phe Glu Gly Ser Leu
485 490 495

Pro Thr Cys Glu Ala Gln Cys Pro Ala Asn Glu Val Arg Thr Gly Ser
500 505 510

Ser Gly Val Ile Leu Ser Pro Gly Tyr Pro Gly Asn Tyr Phe Asn Ser
515 520 525

Gln Thr Cys Ser Trp Ser Ile Lys Val Glu Pro Asn Leu Gln Leu Gly
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Ala Lys Val Asp Phe Val Cys Asp Glu Gly Phe Gln Leu Lys Gly Ser
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Ser Ala Ser Tyr Cys Val Leu Ala Gly Met Glu Ser Asn Tyr Asn Ile
565 570 575

Thr Ile Phe Val Asp Thr Phe Gln Ser Glu Lys Gln Phe Asp Ala Leu
580 585 590

Glu Val Phe Asp Gly Ser Ser Gly Gln Ser Pro Leu Leu Val Val Leu
595 600 605

Ser Gly Asn His Thr Glu Gln Ser Asn Phe Thr Ser Arg Ser Leu Trp
610 615 620

Asn Ser Ser Val Pro Val Cys Glu Gln Ile Phe Cys Pro Ser Pro Pro
625 630 635 640

Val Ile Pro Asn Gly Arg His Thr Gly Lys Pro Leu Glu Val Phe Pro
645 650 655

Phe Gly Lys Asn Gln Leu Tyr Leu Arg Trp Ser Thr Asp His Ala Thr
660 665 670

Ser Lys Lys Gly Phe Lys Ile Arg Tyr Ala Ala Pro Tyr Cys Ser Leu
675 680 685

Thr His Pro Leu Lys Asn Gly Gly Ile Leu Asn Arg Thr Ala Gly Ala
690 695 700

Val Gly Ser Ala Val Asn Tyr Thr Cys Asp Pro His Pro Asp Arg Gly
705 710 715 720

Thr Ser Phe Asp Leu Ile Gly Glu Ser Thr Ile Arg Cys Thr Ser Asp
725 730 735

Pro Gln Gly Asn Gly Val Trp Ser Ser Pro Ala Pro Arg Cys Gly Ile
740 745 750

Leu Gly His Cys Gln Lys Val His Tyr Phe Cys Lys Pro Gly Tyr Arg
755 760 765

Met Val Gly His Ser Asn Ala Thr Cys Arg Arg Asn Pro Leu Gly Met
770 775 780

Tyr Gln Trp Asp Ser Leu Thr Pro Leu Cys Gln Ala Val Ser Cys Gly
785 790 795 800

Ala Pro Asp His Phe Leu Phe Ala Lys Leu Lys Thr Gln Thr Asn Ala
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Ser Asp Phe Pro Ile Gly Thr Ser Leu Lys Tyr Glu Cys Arg Pro Glu
820 825 830

Tyr Tyr Gly Arg Pro Phe Ser Ile Thr Cys Leu Asp Asn Leu Val Ile
835 840 845

Pro Glu Ser Pro Gly Asn Gly Ser Phe Thr Gly Asn Glu Phe Thr Leu
850 855 860

Asp Ser Lys Val Val Tyr Glu Cys His Glu Gly Phe Lys Leu Glu Ser
865 870 875 880

Ser Gln Gln Ala Thr Ala Val Cys Gln Glu Asp Gly Leu Trp Ser Ser
885 890 895

Pro Lys Asp Val Cys Lys Arg Lys Ser Cys Lys Thr Pro Pro Asp Pro
900 905 910

Val Asn Gly Met Val His Val Ile Thr Asp Ile Gln Val Gly Ser Arg
915 920 925

Ile Asn Tyr Ser Cys Thr Thr Trp Ser Asn Lys Gly Lys Pro Pro Thr
930 935 940

Cys Lys Pro Val Ala Cys Pro Ser Ile Glu Ala Gln Leu Ser Glu His
945 950 955 960

Val Ile Trp Arg Leu Val Ser Gly Ser Leu Asn Glu Tyr Gly Ala Gln
965 970 975

Val Leu Leu Ser Cys Ser Pro Gly His Arg Leu Ile Gly His Ser Ser
980 985 990

Ala Glu Cys Ile Leu Ser Gly Asn Ala Ala His Trp Ser Thr Lys Pro
995 1000 1005

Pro Ile Cys Gln Arg Ile Pro Cys Gly Leu Pro Pro Thr Ile Ala
1010 1015 1020

Asn Gly Asp Phe Ile Ser Thr Asn Gly Tyr Tyr Leu Glu Gly Trp
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Arg Leu Leu Arg Cys Gln Ala Asn Gly Thr Trp Asn Ile Gly Asp
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Glu Arg Pro Ser Cys Arg Val Ile Ser Cys Gly Ser Leu Ser Phe
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Arg Lys Val Phe Glu Leu Val Gly Glu Pro Ser Ile Tyr Cys Thr
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Ser Asn Asp Asp Gln Val Gly Ile Trp Ser Gly Pro Ala Pro Gln
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Thr Val Tyr Gly Ala Thr Ala Ile Phe Thr Cys Asn Thr Gly Tyr
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Thr Leu Val Gly Ser His Val Arg Glu Cys Leu Ala Asn Gly Leu
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Trp Ser Gly Ser Glu Thr Arg Cys Ile Xaa Pro Asn Lys Cys Thr
1160 1165 1170

Pro Pro Asn Val Glu Asn Gly Ile Leu Val Ser Asp Asn Arg Ser
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Leu Phe Ser Leu Asn Glu Val Val Glu Phe Arg Cys Gln Pro Gly
1190 1195 1200

Phe Val Met Lys Gly Pro Arg Arg Val Lys Cys Gln Cys Leu Ala
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Gly His Cys Gly Ser Pro Asp Pro Ile Val Asn Gly His Ile Ser
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Gly Asp Gly Phe Ser Tyr Arg Asp Thr Val Val Tyr Gln Cys Asn
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Pro Gly Phe Arg Leu Val Gly Thr Ser Val Arg Ile Cys Leu Ala
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Gln Pro Pro Pro Asp Val Leu His Ala Glu Arg Thr Gln Arg Asp
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Lys Asp Asn Phe Ser Pro Gly Gln Glu Val Phe Tyr Ser Cys Glu
1295 1300 1305

Pro Gly Tyr Gln Asp His Lys Trp Ser Gly Gln Thr Pro Val Cys
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Val Pro Ile Thr Cys Gly His Pro Gly Asn Pro Ala His Gly Phe
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Thr Asn Gly Ser Glu Phe Asn Leu Asn Asp Val Val Asn Phe Thr
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Cys Asn Thr Gly Tyr Asp Leu Arg Gly Ala Ala Ser Met Arg Cys
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Thr Pro Gln Gly Asp Trp Ser Pro Ala Ala Pro Thr Cys Glu Val
1370 1375 1380

Lys Ser Cys Asp Asp Phe Met Gly Gln Leu Leu Asn Gly Arg Val
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Leu Phe Pro Val Asn Leu Gln Leu Leu Gln Gly Val Ser Arg Ala
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Gln Cys Arg Ser Asn Gly Gln Trp Ser Ser Pro Leu Pro Thr Cys
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Arg Val Val Asn Cys Ser Asp Pro Gly Phe Val Glu Asn Ala Ile
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Arg His Gly Gln Gln Asn Phe Pro Glu Ser Phe Glu Leu Gly Ala
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Lys Val Asp Phe Val Cys Asp Glu Gly Phe Gln Leu Lys Gly Ser
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Ser Ser Val Pro Val Cys Glu Gln Ile Phe Cys Pro Ser Pro Pro
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Val Ile Tyr Gly Met Ser Ile Leu Tyr His Cys Lys Lys Gly Phe
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Tyr Leu Leu Gly Ser Ser Ala Leu Thr Cys Met Ala Asn Gly Leu
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Trp Asp Arg Ser Leu Pro Lys Cys Leu Ala Ile Ser Cys Gly His
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Pro Gly Val Pro Pro Asn Gly Arg His Thr Gly Lys Pro Leu Glu
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Val Phe Pro Phe Gly Lys Thr Val Asn Tyr Thr Cys Asp Pro His
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Pro Asp Arg Gly Thr Ser Phe Asp Leu Ile Gly Glu Ser Thr Ile
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Arg Cys Thr Ser Asp Pro Gln Gly Asn Ala Asn Ala Val Leu Thr
1595 1600 1605

Gly Glu Leu Phe Thr Tyr Gly Ala Val Val His Tyr Ser Cys Arg
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Gly Ser Glu Ser Leu Ile Gly Asn Asp Thr Arg Val Cys Gln Glu
1625 1630 1635

Asp Ser His Gly Val Trp Ser Ser Pro Ala Pro Arg Cys Gly Ile
1640 1645 1650

Leu Gly His Cys Gln Ala Pro Asp His Phe Leu Phe Ala Lys Leu
1655 1660 1665

Lys Thr Gln Thr Asn Ala Ser Asp Phe Pro Ile Gly Thr Ser Leu
1670 1675 1680

Lys Tyr Glu Trp Ser Gly Ala Leu Pro His Cys Thr Gly Asn Asn
1685 1690 1695

Pro Gly Phe Cys Gly Asp Pro Gly Thr Pro Ala His Gly Ser Arg
1700 1705 1710

Leu Gly Asp Asp Phe Lys Thr Lys Ser Leu Leu Arg Phe Ser Cys
1715 1720 1725

Arg Pro Glu Tyr Tyr Gly Arg Pro Phe Ser Ile Thr Cys Leu Asp
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Asn Leu Val Trp Ser Ser Pro Lys Asp Val Cys Lys Arg Lys Ser
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Cys Lys Thr Pro Pro Asp Pro Val Asn Gly Met Val His Val Ile
1760 1765 1770

Thr Asp Cys Glu Met Gly His Gln Leu Arg Gly Ser Pro Glu Arg
1775 1780 1785

Thr Cys Leu Leu Asn Gly Ser Trp Ser Gly Leu Gln Pro Val Cys
1790 1795 1800

Glu Ala Val Ser Cys Gly Asn Pro Gly Thr Pro Thr Asn Gly Met
1805 1810 1815

Ile Val Ser Ser Asp Gly Ile Gln Val Gly Ser Arg Ile Asn Tyr
1820 1825 1830

Ser Cys Thr Thr Gly His Arg Leu Ile Gly His Ser Ser Ala Glu
1835 1840 1845

Cys Ile Leu Ser Gly Asn Ala Ala His Trp Ser Thr Lys Pro Pro
1850 1855 1860

Ile Cys Gln Arg Ile Pro Cys Gly Leu Pro Pro Ile Leu Phe Ser
1865 1870 1875

Ser Ser Val Ile Tyr Ala Cys Trp Glu Gly Tyr Lys Thr Ser Gly
1880 1885 1890

Leu Met Thr Arg His Cys Thr Ala Asn Gly Thr Trp Thr Gly Thr
1895 1900 1905

Ala Pro Asp Cys Thr Ile Ile Ser Cys Gly Asp Pro Gly Thr Ile
1910 1915 1920

Ala Asn Gly Asp Phe Ile Ser Thr Asn Arg Glu Asn Phe His Tyr
1925 1930 1935

Gly Ser Val Val Thr Tyr Arg Cys Asn Pro Gly Ser Gly Gly Arg
1940 1945 1950

Lys Val Phe Glu Leu Val Gly Glu Pro Ser Ile Tyr Cys Thr Ser
1955 1960 1965

Asn Asp Asp Thr Leu Ala Asn Gly Ile Gln Phe Gly Thr Asp Phe
1970 1975 1980

Thr Phe Asn Lys Thr Val Ser Tyr Gln Cys Asn Pro Gly Tyr Val
1985 1990 1995

Met Glu Ala Val Thr Ser Ala Thr Ile Arg Cys Thr Lys Asp Gln
2000 2005 2010

Val Gly Ile Trp Ser Gly Pro Ala Pro Gln Cys Ile Xaa Pro Asn
2015 2020 2025

Lys Cys Thr Pro Pro Asn Val Glu Asn Gly Ile Leu Val Ser Asp
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Gln Pro Gly Phe Gly Arg Trp Asn Pro Ser Lys Pro Val Cys Lys
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Ala Val Leu Cys Pro Gln Pro Pro Pro Val Gln Asn Gly Thr Val
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Glu Gly Ser Asp Phe Arg Trp Gly Ser Ser Ile Ser Tyr Ser Cys
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Met Asp Gly Tyr Val Met Lys Gly Pro Arg Arg Val Lys Cys Gln
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Ala Leu Asn Lys Trp Glu Pro Glu Leu Pro Ser Cys Ser Arg Val
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Cys Gln Pro Pro Pro Asp Val Leu His Ala Glu Arg Thr Gln Arg
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Asp Lys Asp Asn Phe Ser Pro Gly Gln Leu Ser His Ser Ala Ile
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Leu Ser Cys Glu Gly Arg Gly Val Trp Lys Gly Glu Ile Pro Gln
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Cys Leu Pro Val Phe Cys Gly Asp Pro Gly Ile Pro Ala Glu Gly
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Arg Leu Ser Gly Lys Ser Phe Thr Tyr Lys Gln Glu Val Phe Tyr
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Phe Phe Gln Cys Lys Ser Pro Phe Ile Leu Val Gly Ser Ser Arg
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Arg Val Cys Gln Ala Asp Gly Thr Trp Ser Gly Ile Gln Pro Thr
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Cys Ile Asp Pro Ala His Asn Thr Cys Pro Asp Pro Gly Thr Pro
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His Asn Gly Arg Val Leu Phe Pro Val Asn Leu Gln Leu Gly Ala
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Lys Val Asp Phe Val Cys Asp Glu Gly Phe Gln Leu Lys Gly Ser
2315 2320 2325

Ser Ala Ser Tyr Cys Val Leu Ala Gly Met Glu Ser Leu Trp Asn
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Ser Ser Val Pro Val Cys Phe Gly Ile Gln Asn Ser Ser Arg Gly
2345 2350 2355

Tyr Glu Val Gly Ser Thr Val Phe Phe Arg Cys Arg Lys Gly Tyr
2360 2365 2370

His Ile Gln Gly Ser Thr Thr Arg Thr Cys Leu Ala Asn Leu Thr
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Trp Ser Gly Ile Gln Thr Glu Cys Glu Gln Ile Phe Cys Pro Ser
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Val Phe Pro Phe Gly Lys Ala Val Asn Tyr Thr Cys Asp Pro His
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Pro Asp Arg Gly Thr Ser Phe Asp Leu Ile Gly Glu Ser Ile Pro
2435 2440 2445

His Ala Cys Arg Gln Pro Glu Thr Pro Ala His Ala Asp Val Arg
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Ala Ile Asp Leu Pro Thr Phe Gly Tyr Thr Leu Val Tyr Thr Cys
2465 2470 2475

His Pro Gly Phe Phe Leu Ala Gly Gly Ser Thr Ile Arg Cys Thr
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Ser Asp Pro Gln Gly Asn Gly Val Trp Ser Ser Pro Ala Pro Arg
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Leu Tyr Val Leu Thr Gly Ser Ser Val Pro Asp Leu Ile Val Ser Met
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Ser Asn Gln Met Trp Leu His Leu Gln Ser Asp Asp Ser Ile Gly Ser
35 40 45

cct ggg ttt aaa gct gtt tac caa gaa att gaa aag gga ggg tgt ggg 192
Pro Gly Phe Lys Ala Val Tyr Gln Glu Ile Glu Lys Gly Gly Cys Gly
50 55 60

gat cct gga atc ccc gcc tat ggg aag cgg acg ggc agc agt ttc ctc 240
Asp Pro Gly Ile Pro Ala Tyr Gly Lys Arg Thr Gly Ser Ser Phe Leu
65 70 75 80

cat gga gat aca ctc acc ttt gaa tgc ccg gcg gcc ttt gag ctg gtg 288
His Gly Asp Thr Leu Thr Phe Glu Cys Pro Ala Ala Phe Glu Leu Val
85 90 95

ggg gag aga gtt atc acc tgt cag cag aac aat cag tgg tct ggc aac 336
Gly Glu Arg Val Ile Thr Cys Gln Gln Asn Asn Gln Trp Ser Gly Asn
100 105 110

aag ccc agc tgt gta ttt tca tgt ttc ttc aac ttt acg gca tca tct 384
Lys Pro Ser Cys Val Phe Ser Cys Phe Phe Asn Phe Thr Ala Ser Ser
115 120 125

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Gly Ile Ile Leu Ser Pro Asn Tyr Pro Glu Glu Tyr Gly Asn Asn Met
    130                 135                 140

aac tgt gtc tgg ttg att atc tcg gag cca gga agt cga att cac cta      480
Asn Cys Val Trp Leu Ile Ile Ser Glu Pro Gly Ser Arg Ile His Leu
145                 150                 155                 160

atc ttt aat gat ttt gat gtt gag cct caa ttt gac ttt ctc gcg gtc      528
Ile Phe Asn Asp Phe Asp Val Glu Pro Gln Phe Asp Phe Leu Ala Val
                165                 170                 175

aag gat gat ggc att tct gac ata act gtc ctg ggt act ttt tct ggc      576
Lys Asp Asp Gly Ile Ser Asp Ile Thr Val Leu Gly Thr Phe Ser Gly
            180                 185                 190

aat gaa gtg cct tcc cag ctg gcc agc agt ggg cat ata gtt cgc ttg      624
Asn Glu Val Pro Ser Gln Leu Ala Ser Ser Gly His Ile Val Arg Leu
        195                 200                 205

gaa ttt cag tct gac cat tcc act act ggc aga ggg ttc aac atc act      672
Glu Phe Gln Ser Asp His Ser Thr Thr Gly Arg Gly Phe Asn Ile Thr
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tac acc aca ttt ggt cag aat gag tgc cat gat cct ggc att cct ata      720
Tyr Thr Thr Phe Gly Gln Asn Glu Cys His Asp Pro Gly Ile Pro Ile
225                 230                 235                 240

aac gga cga cgt ttt ggt gac agg ttt cta ctc ggg agc tcg gtt tct      768
Asn Gly Arg Arg Phe Gly Asp Arg Phe Leu Leu Gly Ser Ser Val Ser
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ttc cac tgt gat gat ggc ttt gtc aag acc cag gga tcc gag tcc att      816
Phe His Cys Asp Asp Gly Phe Val Lys Thr Gln Gly Ser Glu Ser Ile
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acc tgc ata ctg caa gac ggg aac gtg gtc tgg agc tcc acc gtg ccc      864
Thr Cys Ile Leu Gln Asp Gly Asn Val Val Trp Ser Ser Thr Val Pro
        275                 280                 285

cgc tgt gaa gct cca tgt ggt gga cat ctg aca gcg tcc agc gga gtc      912
Arg Cys Glu Ala Pro Cys Gly Gly His Leu Thr Ala Ser Ser Gly Val
    290                 295                 300

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Ile Leu Pro Pro Gly Trp Pro Gly Tyr Tyr Lys Asp Ser Leu His Cys
305                 310                 315                 320

gaa tgg ata att gaa gca aaa cca ggc cac tct atc aaa ata act ttt     1008
Glu Trp Ile Ile Glu Ala Lys Pro Gly His Ser Ile Lys Ile Thr Phe
                325                 330                 335

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Asp Arg Phe Gln Thr Glu Val Asn Tyr Asp Thr Leu Glu Val Arg Asp
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Gly Pro Ala Ser Ser Ser Pro Leu Ile Gly Glu Tyr His Gly Thr Gln
        355                 360                 365

gca ccc cag ttc ctc atc agc acc ggg aac ttc atg tac ctg cta ttc     1152
Ala Pro Gln Phe Leu Ile Ser Thr Gly Asn Phe Met Tyr Leu Leu Phe
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Ser Val Thr Leu Glu Ser Asp Ser Cys Leu Asp Pro Gly Ile Pro Val
405 410 415

aac grc cat cgc cac ggt gga gac ttt ggc atc agg tcc aca gtg act 1296
Asn Xaa His Arg His Gly Gly Asp Phe Gly Ile Arg Ser Thr Val Thr
420 425 430

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Phe Ser Cys Asp Pro Gly Tyr Thr Leu Ser Asp Asp Glu Pro Leu Val
435 440 445

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Cys Glu Arg Asn His Gln Trp Asn His Ala Leu Pro Ser Cys Asp Ala
450 455 460

cta tgt gga ggc tac atc caa ggg aag agt gga aca gtc ctt tct cct 1440
Leu Cys Gly Gly Tyr Ile Gln Gly Lys Ser Gly Thr Val Leu Ser Pro
465 470 475 480

ggg ttt cca gat ttt tat cca aac tct cta aac ygc acg tgg acc att 1488
Gly Phe Pro Asp Phe Tyr Pro Asn Ser Leu Asn Xaa Thr Trp Thr Ile
485 490 495

gaa gtg tct cat ggg aaa gga gtt caa atg atc ttt cac acc ttt cat 1536
Glu Val Ser His Gly Lys Gly Val Gln Met Ile Phe His Thr Phe His
500 505 510

ctt gag agt tcc cac gac tat tta ctg atc aca gag gat gga agt ttt 1584
Leu Glu Ser Ser His Asp Tyr Leu Leu Ile Thr Glu Asp Gly Ser Phe
515 520 525

tcc gag ccc gtt gcc agg ctc acc ggg tcg gtg ttg cct cat acg atc 1632
Ser Glu Pro Val Ala Arg Leu Thr Gly Ser Val Leu Pro His Thr Ile
530 535 540

aag gca ggc ctg ttt gga aac ttc act gcc cag ctt cgg ttt ata tca 1680
Lys Ala Gly Leu Phe Gly Asn Phe Thr Ala Gln Leu Arg Phe Ile Ser
545 550 555 560

gac ttc tca att tcg tac gag ggc ttc aat atc aca ttt tca gaa tat 1728
Asp Phe Ser Ile Ser Tyr Glu Gly Phe Asn Ile Thr Phe Ser Glu Tyr
565 570 575

gac ctg gag cca tgt gat gat cct gga gtc cct gcc ttc agc cga aga 1776
Asp Leu Glu Pro Cys Asp Asp Pro Gly Val Pro Ala Phe Ser Arg Arg
580 585 590

att ggt ttt cac ttt ggt gtg gga gac tct ctg acg ttt tcc tgc ttc 1824
Ile Gly Phe His Phe Gly Val Gly Asp Ser Leu Thr Phe Ser Cys Phe
595 600 605

ctg gga tat cgt tta gaa ggt gcc rcc aag ctt acc tgc ctg ggt ggg 1872
Leu Gly Tyr Arg Leu Glu Gly Ala Xaa Lys Leu Thr Cys Leu Gly Gly
610 615 620

ggc cgc cgt gtg tgg agt gca cct ctg cca agg tgt gtg gcc gaa tgt 1920
Gly Arg Arg Val Trp Ser Ala Pro Leu Pro Arg Cys Val Ala Glu Cys
625 630 635 640

gga gca agt gtc aaa gga aat gaa gga aca tta ctg tct cca aat ttt 1968
Gly Ala Ser Val Lys Gly Asn Glu Gly Thr Leu Leu Ser Pro Asn Phe
645 650 655

cca tcc aat tat gat aat aac cat gag tgt atc tat aaa ata gaa aca 2016
Pro Ser Asn Tyr Asp Asn Asn His Glu Cys Ile Tyr Lys Ile Glu Thr
660 665 670

gaa gcc ggc aag ggc atc cac ctt aga aca cga agc ttc cag ctg ttt 2064
Glu Ala Gly Lys Gly Ile His Leu Arg Thr Arg Ser Phe Gln Leu Phe
675 680 685

gaa gga gat act cta aag gta tat gat gga aaa gac agt tcc tca cgt 2112
Glu Gly Asp Thr Leu Lys Val Tyr Asp Gly Lys Asp Ser Ser Ser Arg
690 695 700

cca ctg ggc acg ttc act aaa aat gaa ctt ctg ggg ctg atc cta aac 2160
Pro Leu Gly Thr Phe Thr Lys Asn Glu Leu Leu Gly Leu Ile Leu Asn
705 710 715 720

agc aca tcc aat cac ctr tgg cta gag ttc aac acc aat gga tct gac 2208
Ser Thr Ser Asn His Xaa Trp Leu Glu Phe Asn Thr Asn Gly Ser Asp
725 730 735

acc gac caa ggt ttt caa ctc acc tat acc agt ttt gat ctg gta aaa 2256
Thr Asp Gln Gly Phe Gln Leu Thr Tyr Thr Ser Phe Asp Leu Val Lys
740 745 750

tgt gag gat ccg ggc atc cct aac tac ggc tat agg atc cgt gat gaa 2304
Cys Glu Asp Pro Gly Ile Pro Asn Tyr Gly Tyr Arg Ile Arg Asp Glu
755 760 765

ggc cac ttt acc gac act gta gtt ctg tac agt tgc aac ccg ggg tac 2352
Gly His Phe Thr Asp Thr Val Val Leu Tyr Ser Cys Asn Pro Gly Tyr
770 775 780

gcc atg cat ggc agc aac acc ctg acc tgt ttg agt gga gac agg aga 2400
Ala Met His Gly Ser Asn Thr Leu Thr Cys Leu Ser Gly Asp Arg Arg
785 790 795 800

gtg tgg gac aaa cca cta cct tcg tgc ata gcg gaa tgt ggt ggt cag 2448
Val Trp Asp Lys Pro Leu Pro Ser Cys Ile Ala Glu Cys Gly Gly Gln
805 810 815

atc cat gca gcc aca tca gga cga ata ttg tcc cct ggc tat cca gct 2496
Ile His Ala Ala Thr Ser Gly Arg Ile Leu Ser Pro Gly Tyr Pro Ala
820 825 830

ccg tat gac aac aac ctc cac tgc acc tgg att ata gag gca gac cca 2544
Pro Tyr Asp Asn Asn Leu His Cys Thr Trp Ile Ile Glu Ala Asp Pro
835 840 845

gga aag acc att agc ctc cat ttc att gtt ttc gac acg gag atg gct 2592
Gly Lys Thr Ile Ser Leu His Phe Ile Val Phe Asp Thr Glu Met Ala
850 855 860

cac gac atc ctc aag gtc tgg gac ggg ccg gtg gac agt gac atc ctg 2640
His Asp Ile Leu Lys Val Trp Asp Gly Pro Val Asp Ser Asp Ile Leu
865 870 875 880

ctg aag gag tgg agt ggc tcc gcc ctt ccg gag gac atc cac agc acc 2688
Leu Lys Glu Trp Ser Gly Ser Ala Leu Pro Glu Asp Ile His Ser Thr
885 890 895

ttc aac tca ctc acc ctg cag ttc gac agc gac ttc ttc atc agc aag 2736
Phe Asn Ser Leu Thr Leu Gln Phe Asp Ser Asp Phe Phe Ile Ser Lys
900 905 910

tct ggc ttc tcc atc cag ttc tcc acc tca att gca gcc acc tgt aac 2784
Ser Gly Phe Ser Ile Gln Phe Ser Thr Ser Ile Ala Ala Thr Cys Asn
915 920 925

gat cca ggt atg ccc caa aat ggc acc cgc tat gga gac agc aga gag 2832
Asp Pro Gly Met Pro Gln Asn Gly Thr Arg Tyr Gly Asp Ser Arg Glu
930 935 940

gct gga gac acc gtc aca ttc cag tgt gac cct ggc tat cag ctc caa 2880
Ala Gly Asp Thr Val Thr Phe Gln Cys Asp Pro Gly Tyr Gln Leu Gln
945 950 955 960

gga caa gcc aaa atc acc tgt gtg cag ctg aat aac cgg ttc ttt tgg 2928
Gly Gln Ala Lys Ile Thr Cys Val Gln Leu Asn Asn Arg Phe Phe Trp
965 970 975

caa cca gac cct cct aca tgc ata gct gct tgt gga ggg aat ctg acg 2976
Gln Pro Asp Pro Pro Thr Cys Ile Ala Ala Cys Gly Gly Asn Leu Thr
980 985 990

ggc cca gca ggt gtt att ttg tca ccc aac tac cca cag ccg tat cct 3024
Gly Pro Ala Gly Val Ile Leu Ser Pro Asn Tyr Pro Gln Pro Tyr Pro
995 1000 1005

cct ggg aag gaa tgt gac tgg aga gta aaa gtg aac ccg gac ttt 3069
Pro Gly Lys Glu Cys Asp Trp Arg Val Lys Val Asn Pro Asp Phe
1010 1015 1020

gtc atc gcc ttg ata ttc aaa agt ttc aac atg gag ccc agc tat 3114
Val Ile Ala Leu Ile Phe Lys Ser Phe Asn Met Glu Pro Ser Tyr
1025 1030 1035

gac ttc cta cac atc tat gaa ggg gaa gat tcc aac agc ccc ctc 3159
Asp Phe Leu His Ile Tyr Glu Gly Glu Asp Ser Asn Ser Pro Leu
1040 1045 1050

att ggg agt tac cag ggc tct cag gcc cca gaa aga ata gag agt 3204
Ile Gly Ser Tyr Gln Gly Ser Gln Ala Pro Glu Arg Ile Glu Ser
1055 1060 1065

agc gga aac agc ctg ttt ctg gca ttt cgg agt gat gcc tcc gtg 3249
Ser Gly Asn Ser Leu Phe Leu Ala Phe Arg Ser Asp Ala Ser Val
1070 1075 1080

ggc ctt tca ggg ttc gcc att gaa ttt aaa gag aaa cca cgg gaa 3294
Gly Leu Ser Gly Phe Ala Ile Glu Phe Lys Glu Lys Pro Arg Glu
1085 1090 1095

gct tgt ttt gac cca gga aat ata atg aat ggg aca aga gtt gga 3339
Ala Cys Phe Asp Pro Gly Asn Ile Met Asn Gly Thr Arg Val Gly
1100 1105 1110

aca gac ttc aag ctt ggc tcc acc atc acc tac cag tgt gac tct 3384
Thr Asp Phe Lys Leu Gly Ser Thr Ile Thr Tyr Gln Cys Asp Ser
1115 1120 1125

ggc tat aag att ctt gac ccc tca tcc atc acc tgt gtg att ggg 3429
Gly Tyr Lys Ile Leu Asp Pro Ser Ser Ile Thr Cys Val Ile Gly
1130 1135 1140

gct gat ggg aaa ccc tcc tgg gac caa gtg ctg ccc tcc tgc aat 3474
Ala Asp Gly Lys Pro Ser Trp Asp Gln Val Leu Pro Ser Cys Asn
1145 1150 1155

gct ccc tgt gga ggc cag tac acg gga tca gaa ggg gta gtt tta 3519
Ala Pro Cys Gly Gly Gln Tyr Thr Gly Ser Glu Gly Val Val Leu
1160 1165 1170

tca cca aac tac ccc cat aat tac aca gct ggt caa ata tgc ctc 3564
Ser Pro Asn Tyr Pro His Asn Tyr Thr Ala Gly Gln Ile Cys Leu
1175 1180 1185

tat tcc atc acg gta cca aag gaa ttc gtg gtc ttt gga cag ttt 3609
Tyr Ser Ile Thr Val Pro Lys Glu Phe Val Val Phe Gly Gln Phe
1190 1195 1200

gcc tat ttc cag aca gcc ctg aat gat ttg gca gaa tta ttt gat 3654
Ala Tyr Phe Gln Thr Ala Leu Asn Asp Leu Ala Glu Leu Phe Asp
1205 1210 1215

gga acc cat gca cag gcc aga ctt ctc agc tca ctc tcg ggg tct 3699
Gly Thr His Ala Gln Ala Arg Leu Leu Ser Ser Leu Ser Gly Ser
1220 1225 1230

cac tca ggg gaa aca ttg ccc ttg gct acg tca aat caa att ctg 3744
His Ser Gly Glu Thr Leu Pro Leu Ala Thr Ser Asn Gln Ile Leu
1235 1240 1245

ctc cga ttc agt gca aag agc ggt gcc tct gcc cgc ggc ttc cac 3789
Leu Arg Phe Ser Ala Lys Ser Gly Ala Ser Ala Arg Gly Phe His
1250 1255 1260

ttc gtg tat caa gct gtt cct cgt acc agt gac acc caa tgc agc 3834
Phe Val Tyr Gln Ala Val Pro Arg Thr Ser Asp Thr Gln Cys Ser
1265 1270 1275

tct gtc ccc gag ccc aga tac gga agg aga att ggt tct gag ttt 3879
Ser Val Pro Glu Pro Arg Tyr Gly Arg Arg Ile Gly Ser Glu Phe
1280 1285 1290

tct gcc ggc tcc atc gtc cga ttc gag trc aac ccg gga tac ctg 3924
Ser Ala Gly Ser Ile Val Arg Phe Glu Xaa Asn Pro Gly Tyr Leu
1295 1300 1305

ctt cag ggt tcc acg gcg ctc cac tgc cag tcc gtg ccc aac gcc 3969
Leu Gln Gly Ser Thr Ala Leu His Cys Gln Ser Val Pro Asn Ala
1310 1315 1320

ttg gca cag tgg aac gac acg atc ccc agc tgt gtg gta ccc tgc 4014
Leu Ala Gln Trp Asn Asp Thr Ile Pro Ser Cys Val Val Pro Cys
1325 1330 1335

agt ggc aat ttc act caa cga aga ggt aca atc ctg tcc ccc ggc 4059
Ser Gly Asn Phe Thr Gln Arg Arg Gly Thr Ile Leu Ser Pro Gly
1340 1345 1350

tac cct gag cca tac gga aac aac ttg aac tgt ata tgg aag atc 4104
Tyr Pro Glu Pro Tyr Gly Asn Asn Leu Asn Cys Ile Trp Lys Ile
1355 1360 1365

ata gtt acg gag ggc tcg gga att cag atc caa gtg atc agt ttt 4149
Ile Val Thr Glu Gly Ser Gly Ile Gln Ile Gln Val Ile Ser Phe
1370 1375 1380

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gcc acg gag cag aac tgg gac tcc ctt gag atc cac gat ggt ggg     4194
Ala Thr Glu Gln Asn Trp Asp Ser Leu Glu Ile His Asp Gly Gly
    1385                1390                1395

gat gtg acc gca ccc aga ctg gga agc ttc tca ggc acc aca gta     4239
Asp Val Thr Ala Pro Arg Leu Gly Ser Phe Ser Gly Thr Thr Val
    1400                1405                1410

ccg gca ctg ctg aac agt act tcc aac caa ctc tac ctg cat ttc     4284
Pro Ala Leu Leu Asn Ser Thr Ser Asn Gln Leu Tyr Leu His Phe
    1415                1420                1425

cag tct gac att agt gtg gca gct gct ggt ttc cac ctg gaa tac     4329
Gln Ser Asp Ile Ser Val Ala Ala Ala Gly Phe His Leu Glu Tyr
    1430                1435                1440

aaa act gta ggt ctt gct gca tgc caa gaa cca gcc ctc ccc agc     4374
Lys Thr Val Gly Leu Ala Ala Cys Gln Glu Pro Ala Leu Pro Ser
    1445                1450                1455

aac agc atc aaa atc gga gat cgg tac atg gtg aac gac gtg ctc     4419
Asn Ser Ile Lys Ile Gly Asp Arg Tyr Met Val Asn Asp Val Leu
    1460                1465                1470

tcc ttc cag tgc gag ccc ggg tac acc ctg cag ggc cgt tcc cac     4464
Ser Phe Gln Cys Glu Pro Gly Tyr Thr Leu Gln Gly Arg Ser His
    1475                1480                1485

att tcc tgt atg cca ggg acc gtt cgc cgt tgg aac tat ccg tct     4509
Ile Ser Cys Met Pro Gly Thr Val Arg Arg Trp Asn Tyr Pro Ser
    1490                1495                1500

ccc ctg tgc att gca acc tgt gga ggg acg ctg agc acc ttg ggt     4554
Pro Leu Cys Ile Ala Thr Cys Gly Gly Thr Leu Ser Thr Leu Gly
    1505                1510                1515

ggt gtg atc ctg agc ccc ggc ttc cca ggt tct tac ccc aac aac     4599
Gly Val Ile Leu Ser Pro Gly Phe Pro Gly Ser Tyr Pro Asn Asn
    1520                1525                1530

tta gac tgc acc tgg agg atc tca tta ccc atc ggc tat ggt gca     4644
Leu Asp Cys Thr Trp Arg Ile Ser Leu Pro Ile Gly Tyr Gly Ala
    1535                1540                1545

cat att cag ttt ctg aat ttt tct acc gaa gct aat cat gac ttc     4689
His Ile Gln Phe Leu Asn Phe Ser Thr Glu Ala Asn His Asp Phe
    1550                1555                1560

ctt gaa att caa aat gga cct tac cac acc agc ccc atg att gga     4734
Leu Glu Ile Gln Asn Gly Pro Tyr His Thr Ser Pro Met Ile Gly
    1565                1570                1575

caa ttt agc ggc acg gat ctc ccc gcg gcc ctg ctg agc aca acg     4779
Gln Phe Ser Gly Thr Asp Leu Pro Ala Ala Leu Leu Ser Thr Thr
    1580                1585                1590

cat gaa acc ctc atc cac ttt tat agt gac cat tcg caa aac cgg     4824
His Glu Thr Leu Ile His Phe Tyr Ser Asp His Ser Gln Asn Arg
    1595                1600                1605

caa gga ttt aaa ctt gct tac caa gcc tat gaa tta cag aac tgt     4869
Gln Gly Phe Lys Leu Ala Tyr Gln Ala Tyr Glu Leu Gln Asn Cys
    1610                1615                1620
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cca gat  cca ccc cca ttt cag  aat ggg tac atg atc  aac tcg gat    4914
Pro Asp  Pro Pro Pro Phe Gln  Asn Gly Tyr Met Ile  Asn Ser Asp
    1625                 1630                 1635

tac agc  gtg ggg caa tca gta  tct ttc gag tgt tat  cct ggg tac    4959
Tyr Ser  Val Gly Gln Ser Val  Ser Phe Glu Cys Tyr  Pro Gly Tyr
    1640                 1645                 1650

att cta  ata ggc cat cct gtc  ctc act tgt cag cat  ggg atc aac    5004
Ile Leu  Ile Gly His Pro Val  Leu Thr Cys Gln His  Gly Ile Asn
    1655                 1660                 1665

aga aac  tgg aac tac cct ttt  cca aga tgt gat gcc  cct tgt ggg    5049
Arg Asn  Trp Asn Tyr Pro Phe  Pro Arg Cys Asp Ala  Pro Cys Gly
    1670                 1675                 1680

tac aac  gta act tct cag aac  ggc acc atc tac tcc  cct ggc ttt    5094
Tyr Asn  Val Thr Ser Gln Asn  Gly Thr Ile Tyr Ser  Pro Gly Phe
    1685                 1690                 1695

cct gat  gag tat ccg atc ctg  aag gac tgc att tgg  ctc atc acg    5139
Pro Asp  Glu Tyr Pro Ile Leu  Lys Asp Cys Ile Trp  Leu Ile Thr
    1700                 1705                 1710

gtg cct  cca ggg cac gga gtt  tac atc aac ttc acc  ctg tta cag    5184
Val Pro  Pro Gly His Gly Val  Tyr Ile Asn Phe Thr  Leu Leu Gln
    1715                 1720                 1725

acg gaa  gct gtc aac gat tac  att gct gtt tgg gac  ggt ccc gat    5229
Thr Glu  Ala Val Asn Asp Tyr  Ile Ala Val Trp Asp  Gly Pro Asp
    1730                 1735                 1740

cag aac  tca ccc cag ctg gga  gtt ttc agt ggc aac  aca gcc ctc    5274
Gln Asn  Ser Pro Gln Leu Gly  Val Phe Ser Gly Asn  Thr Ala Leu
    1745                 1750                 1755

gaa acg  gcg tat agc tcc acc  aac caa gtc ctg ctc  aag ttc cac    5319
Glu Thr  Ala Tyr Ser Ser Thr  Asn Gln Val Leu Leu  Lys Phe His
    1760                 1765                 1770

agc gac  ttt tca aat gga ggc  ttc ttt gtc ctc aat  ttc cac gca    5364
Ser Asp  Phe Ser Asn Gly Gly  Phe Phe Val Leu Asn  Phe His Ala
    1775                 1780                 1785

ttt cag  ctc aag aaa tgt caa  cct ccc cca gcg gtt  cca cag gca    5409
Phe Gln  Leu Lys Lys Cys Gln  Pro Pro Pro Ala Val  Pro Gln Ala
    1790                 1795                 1800

gaa atg  ctt act gag gat gat  gat ttc gag ata gga  gat ttt gtg    5454
Glu Met  Leu Thr Glu Asp Asp  Asp Phe Glu Ile Gly  Asp Phe Val
    1805                 1810                 1815

aag tac  cag tgc cac ccc ggg  tac acc ttg gtg ggg  acc gac att    5499
Lys Tyr  Gln Cys His Pro Gly  Tyr Thr Leu Val Gly  Thr Asp Ile
    1820                 1825                 1830

ctg act  tgc aag ctc agt tcc  cag ttg cag ttt gag  ggt tct ctc    5544
Leu Thr  Cys Lys Leu Ser Ser  Gln Leu Gln Phe Glu  Gly Ser Leu
    1835                 1840                 1845

cca aca  tgt gaa gca caa tgc  cca gca aat gaa gtc  cgg act gga    5589
Pro Thr  Cys Glu Ala Gln Cys  Pro Ala Asn Glu Val  Arg Thr Gly
    1850                 1855                 1860
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tca tcg gga gtc att ctc agt cca ggg tat ccg ggt aat tat ttt     5634
Ser Ser Gly Val Ile Leu Ser Pro Gly Tyr Pro Gly Asn Tyr Phe
    1865                1870                1875

aac tcc cag act tgc tct tgg agt att aaa gtg gaa cca aac tac     5679
Asn Ser Gln Thr Cys Ser Trp Ser Ile Lys Val Glu Pro Asn Tyr
    1880                1885                1890

aac att acc atc ttt gtg gac aca ttt caa agt gaa aag cag ttt     5724
Asn Ile Thr Ile Phe Val Asp Thr Phe Gln Ser Glu Lys Gln Phe
    1895                1900                1905

gat gca ctg gaa gtg ttt gat ggt tct tct ggg caa agt cct ctg     5769
Asp Ala Leu Glu Val Phe Asp Gly Ser Ser Gly Gln Ser Pro Leu
    1910                1915                1920

cta gta gtc tta agt ggg aat cat act gaa caa tca aat ttt aca     5814
Leu Val Val Leu Ser Gly Asn His Thr Glu Gln Ser Asn Phe Thr
    1925                1930                1935

agc agg agt aat cag tta tat ctc cgc tgg tcc act gac cat gcc     5859
Ser Arg Ser Asn Gln Leu Tyr Leu Arg Trp Ser Thr Asp His Ala
    1940                1945                1950

acc agt aag aaa gga ttc aag att cgc tat gca gca cct tac tgc     5904
Thr Ser Lys Lys Gly Phe Lys Ile Arg Tyr Ala Ala Pro Tyr Cys
    1955                1960                1965

agt ttg acc cac ccc ctg aag aat ggg ggt att cta aac agg act     5949
Ser Leu Thr His Pro Leu Lys Asn Gly Gly Ile Leu Asn Arg Thr
    1970                1975                1980

gca gga gcg gtt gga agc aaa gtg cat tat ttt tgc aag cct gga     5994
Ala Gly Ala Val Gly Ser Lys Val His Tyr Phe Cys Lys Pro Gly
    1985                1990                1995

tac cga atg gtc ggc cac agc aat gca acc tgt aga cga aac cca     6039
Tyr Arg Met Val Gly His Ser Asn Ala Thr Cys Arg Arg Asn Pro
    2000                2005                2010

ctt ggc atg tac cag tgg gac tcc ctc acg cca ctc tgc cag gct     6084
Leu Gly Met Tyr Gln Trp Asp Ser Leu Thr Pro Leu Cys Gln Ala
    2015                2020                2025

gtg tcc tgt gga atc cca gaa tcc cca gga aac ggt tca ttt acc     6129
Val Ser Cys Gly Ile Pro Glu Ser Pro Gly Asn Gly Ser Phe Thr
    2030                2035                2040

ggg aac gag ttc act ttg gac agt aaa gtg gtc tat gaa tgt cat     6174
Gly Asn Glu Phe Thr Leu Asp Ser Lys Val Val Tyr Glu Cys His
    2045                2050                2055

gag ggc ttc aag ctt gaa tcc agc cag caa gca aca gcc gtg tgt     6219
Glu Gly Phe Lys Leu Glu Ser Ser Gln Gln Ala Thr Ala Val Cys
    2060                2065                2070

caa gaa gat ggg ctg tgg agt aac aag ggg aag ccg ccc acg tgt     6264
Gln Glu Asp Gly Leu Trp Ser Asn Lys Gly Lys Pro Pro Thr Cys
    2075                2080                2085

aag ccg gtc gct tgc ccc agc att gaa gct cag ctc tca gaa cat     6309
Lys Pro Val Ala Cys Pro Ser Ile Glu Ala Gln Leu Ser Glu His
    2090                2095                2100
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gtc atc tgg agg ctg gtt tca gga tcc ttg aat gag tac ggt gct 6354
Val Ile Trp Arg Leu Val Ser Gly Ser Leu Asn Glu Tyr Gly Ala
2105 2110 2115

caa gta ttg ctg agc tgc agt cct ggt tac tac tta gaa ggc tgg 6399
Gln Val Leu Leu Ser Cys Ser Pro Gly Tyr Tyr Leu Glu Gly Trp
2120 2125 2130

agg ctc ctg cgg tgc cag gcc aat ggg acg tgg aac ata gga gat 6444
Arg Leu Leu Arg Cys Gln Ala Asn Gly Thr Trp Asn Ile Gly Asp
2135 2140 2145

gag agg cca agc tgt cga gtt atc tcg tgt gga agc ctt tcc ttt 6489
Glu Arg Pro Ser Cys Arg Val Ile Ser Cys Gly Ser Leu Ser Phe
2150 2155 2160

ccc cca aat ggc aac aag att gga acg ttg aca gtt tat ggg gcc 6534
Pro Pro Asn Gly Asn Lys Ile Gly Thr Leu Thr Val Tyr Gly Ala
2165 2170 2175

aca gct ata ttt acg tgc aac acc ggc tac acg ctt gtg ggg tct 6579
Thr Ala Ile Phe Thr Cys Asn Thr Gly Tyr Thr Leu Val Gly Ser
2180 2185 2190

cat gtc aga gag tgc ttg gca aat ggg ctc tgg agc ggc agc gaa 6624
His Val Arg Glu Cys Leu Ala Asn Gly Leu Trp Ser Gly Ser Glu
2195 2200 2205

act cga tgt ctg gct ggc cac tgc ggt tcc cca gac ccg att gtg 6669
Thr Arg Cys Leu Ala Gly His Cys Gly Ser Pro Asp Pro Ile Val
2210 2215 2220

aac ggt cac att agt gga gat ggc ttc agt tac aga gac acg gtg 6714
Asn Gly His Ile Ser Gly Asp Gly Phe Ser Tyr Arg Asp Thr Val
2225 2230 2235

gtt tac cag tgc aat cct ggt ttc cgg ctt gtg gga act tcc gtg 6759
Val Tyr Gln Cys Asn Pro Gly Phe Arg Leu Val Gly Thr Ser Val
2240 2245 2250

agg ata tgc ctg caa gac cac aag tgg tct gga caa acg cct gtc 6804
Arg Ile Cys Leu Gln Asp His Lys Trp Ser Gly Gln Thr Pro Val
2255 2260 2265

tgt gtc ccc atc aca tgt ggt cac cct gga aac cct gcc cac gga 6849
Cys Val Pro Ile Thr Cys Gly His Pro Gly Asn Pro Ala His Gly
2270 2275 2280

ttc act aat ggc agt gag ttc aac ctg aat gat gtc gtg aat ttc 6894
Phe Thr Asn Gly Ser Glu Phe Asn Leu Asn Asp Val Val Asn Phe
2285 2290 2295

acc tgc aac acg ggc tat ttg ctg cag ggc gtg tct cga gcc cag 6939
Thr Cys Asn Thr Gly Tyr Leu Leu Gln Gly Val Ser Arg Ala Gln
2300 2305 2310

tgt cgg agc aac ggc cag tgg agt agc cct ctg ccc acg tgt cga 6984
Cys Arg Ser Asn Gly Gln Trp Ser Ser Pro Leu Pro Thr Cys Arg
2315 2320 2325

gtg gtg aac tgt tct gat cca ggc ttt gtg gaa aat gcc att cgt 7029
Val Val Asn Cys Ser Asp Pro Gly Phe Val Glu Asn Ala Ile Arg
2330 2335 2340

cac ggg caa cag aac ttc cct gag agt ttt gag tat gga atg agt 7074
His Gly Gln Gln Asn Phe Pro Glu Ser Phe Glu Tyr Gly Met Ser
2345 2350 2355

atc ctg tac cat tgc aag aag gga ttt tac ttg ctg gga tct tca 7119
Ile Leu Tyr His Cys Lys Lys Gly Phe Tyr Leu Leu Gly Ser Ser
2360 2365 2370

gcc ttg acc tgt atg gca aat ggc tta tgg gac cga tcc ctg ccc 7164
Ala Leu Thr Cys Met Ala Asn Gly Leu Trp Asp Arg Ser Leu Pro
2375 2380 2385

aag tgt ttg gct ata tcg tgt gga cac cca ggg gtc cct gcc aac 7209
Lys Cys Leu Ala Ile Ser Cys Gly His Pro Gly Val Pro Ala Asn
2390 2395 2400

gcc gtc ctc act gga gag ctg ttt acc tat ggc gcc gtc gtg cac 7254
Ala Val Leu Thr Gly Glu Leu Phe Thr Tyr Gly Ala Val Val His
2405 2410 2415

tac tcc tgc aga ggg agc gag agc ctc ata ggc aac gac acg aga 7299
Tyr Ser Cys Arg Gly Ser Glu Ser Leu Ile Gly Asn Asp Thr Arg
2420 2425 2430

gtg tgc cag gaa gac agt cac tgg agc ggg gca ctg ccc cac tgc 7344
Val Cys Gln Glu Asp Ser His Trp Ser Gly Ala Leu Pro His Cys
2435 2440 2445

aca gga aat aat cct gga ttc tgt ggt gat ccg ggg acc cca gca 7389
Thr Gly Asn Asn Pro Gly Phe Cys Gly Asp Pro Gly Thr Pro Ala
2450 2455 2460

cat ggg tct cgg ctt ggt gat gac ttt aag aca aag agt ctt ctc 7434
His Gly Ser Arg Leu Gly Asp Asp Phe Lys Thr Lys Ser Leu Leu
2465 2470 2475

cgc ttc tcc tgt gaa atg ggg cac cag ctg agg ggc tcc cct gaa 7479
Arg Phe Ser Cys Glu Met Gly His Gln Leu Arg Gly Ser Pro Glu
2480 2485 2490

cgc acg tgt ttg ctc aat ggg tca tgg tca gga ctg cag ccg gtg 7524
Arg Thr Cys Leu Leu Asn Gly Ser Trp Ser Gly Leu Gln Pro Val
2495 2500 2505

tgt gag gcc gtg tcc tgt ggc aac cct ggc aca ccc acc aac gga 7569
Cys Glu Ala Val Ser Cys Gly Asn Pro Gly Thr Pro Thr Asn Gly
2510 2515 2520

atg att gtc agt agt gat ggc att ctg ttc tcc agc tcg gtc atc 7614
Met Ile Val Ser Ser Asp Gly Ile Leu Phe Ser Ser Ser Val Ile
2525 2530 2535

tat gcc tgc tgg gaa ggc tac aag acc tca ggg ctc atg aca cgg 7659
Tyr Ala Cys Trp Glu Gly Tyr Lys Thr Ser Gly Leu Met Thr Arg
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cat tgc aca gcc aat ggg acc tgg aca ggc act gct ccc gac tgc 7704
His Cys Thr Ala Asn Gly Thr Trp Thr Gly Thr Ala Pro Asp Cys
2555 2560 2565

aca att ata agt tgt ggg gat cca ggc aca cta gca aat ggc atc 7749
Thr Ile Ile Ser Cys Gly Asp Pro Gly Thr Leu Ala Asn Gly Ile
2570 2575 2580

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cag tttggg acc gac ttc acc ttc aac aag act gtg agc tat cag 7794
Gln Phe Gly Thr Asp Phe Thr Phe Asn Lys Thr Val Ser Tyr Gln
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Cys Asn Pro Gly Tyr Val Met Glu Ala Val Thr Ser Ala Thr Ile
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cgc tgt acc aaa gac ggc agg tgg aat ccg agc aaa cct gtc tgc 7884
Arg Cys Thr Lys Asp Gly Arg Trp Asn Pro Ser Lys Pro Val Cys
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aaa gcc gtg ctg tgt cct cag ccg ccg ccg gtg cag aat gga aca 7929
Lys Ala Val Leu Cys Pro Gln Pro Pro Pro Val Gln Asn Gly Thr
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gtg gag gga agt gat ttc cgc tgg ggc tcc agc ata agt tac agc 7974
Val Glu Gly Ser Asp Phe Arg Trp Gly Ser Ser Ile Ser Tyr Ser
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tgc atg gac ggt tac cag ctc tct cac tcc gcc atc ctc tcc tgt 8019
Cys Met Asp Gly Tyr Gln Leu Ser His Ser Ala Ile Leu Ser Cys
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gaa ggt cgc ggg gtg tgg aaa gga gag atc ccc cag tgt ctc cct 8064
Glu Gly Arg Gly Val Trp Lys Gly Glu Ile Pro Gln Cys Leu Pro
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Val Phe Cys Gly Asp Pro Gly Ile Pro Ala Glu Gly Arg Leu Ser
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ggg aaa agt ttc acc tat aag tcc gaa gtc ttc ttc cag tgc aaa 8154
Gly Lys Ser Phe Thr Tyr Lys Ser Glu Val Phe Phe Gln Cys Lys
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tct cca ttt ata ctc gtg gga tcc tcc aga aga gtc tgc caa gct 8199
Ser Pro Phe Ile Leu Val Gly Ser Ser Arg Arg Val Cys Gln Ala
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Asp Gly Thr Trp Ser Gly Ile Gln Pro Thr Cys Ile Asp Pro Ala
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cat aac acc tgc cca gac cct ggt acg cca cac ttt gga ata cag 8289
His Asn Thr Cys Pro Asp Pro Gly Thr Pro His Phe Gly Ile Gln
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aat agc tcc aga ggc tat gag gtt gga agc acg gtt ttt ttc agg 8334
Asn Ser Ser Arg Gly Tyr Glu Val Gly Ser Thr Val Phe Phe Arg
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tgc aga aaa ggc tac cat att caa ggt tcc acg act cgc acc tgc 8379
Cys Arg Lys Gly Tyr His Ile Gln Gly Ser Thr Thr Arg Thr Cys
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ctt gcc aat tta aca tgg agt ggg ata cag acc gaa tgt ata cct 8424
Leu Ala Asn Leu Thr Trp Ser Gly Ile Gln Thr Glu Cys Ile Pro
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His Ala Cys Arg Gln Pro Glu Thr Pro Ala His Ala Asp Val Arg
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His Pro Gly Phe Phe Leu Ala Gly Gly Ser Glu His Arg Thr Cys
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aaa gca gac atg aaa tgg aca gga aag tcg cct gtg tgt aaa agt      8604
Lys Ala Asp Met Lys Trp Thr Gly Lys Ser Pro Val Cys Lys Ser
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Lys Gly Val Arg Glu Val Asn Glu Thr Val Thr Lys Thr Pro Val
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Pro Ser Asp Val Phe Phe Val Asn Ser Leu Trp Lys Gly Tyr Tyr
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gaa tat tta ggg aaa aga caa ccc gcc act cta act gtt gac tgg      8739
Glu Tyr Leu Gly Lys Arg Gln Pro Ala Thr Leu Thr Val Asp Trp
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Phe Asn Ala Thr Ser Ser Lys Val Asn Ala Thr Phe Ser Glu Ala
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tcg cca gtg gag ctg aag ttg aca ggc att tac aag aag gag gag      8829
Ser Pro Val Glu Leu Lys Leu Thr Gly Ile Tyr Lys Lys Glu Glu
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Ala His Leu Leu Leu Lys Ala Phe Gln Ile Lys Gly Gln Ala Asp
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Ile Phe Val Ser Lys Phe Glu Asn Asp Asn Trp Gly Leu Asp Gly
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Tyr Val Ser Ser Gly Leu Glu Arg Gly Gly Phe Thr Phe Gln Gly
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Asp Ile His Gly Lys Asp Phe Gly Lys Phe Lys Leu Glu Arg Gln
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Asp Pro Leu Asn Pro Asp Gln Asp Ser Ser Ser His Tyr His Gly
    3005                3010                3015

acc agc agt ggc tct gtg gcg gct gcc att ctg gtt cct ttc ttt      9099
Thr Ser Ser Gly Ser Val Ala Ala Ala Ile Leu Val Pro Phe Phe
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Ala Leu Ile Leu Ser Gly Phe Ala Phe Tyr Leu Tyr Lys His Arg
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tta aaa ccc aca gaa gcc aag gct gtg agg ttt gac aca act ctg      9279
Leu Lys Pro Thr Glu Ala Lys Ala Val Arg Phe Asp Thr Thr Leu
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aac aca gtc tgt aca gtg gta tagccctcag tgccccaaca ggactgattc     9330
Asn Thr Val Cys Thr Val Val
    3095                3100

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<212> PRT

<213> Homo sapiens

<400> 7

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20 25 30

Ser Asn Gln Met Trp Leu His Leu Gln Ser Asp Asp Ser Ile Gly Ser
35 40 45

Pro Gly Phe Lys Ala Val Tyr Gln Glu Ile Glu Lys Gly Gly Cys Gly
50 55 60

Asp Pro Gly Ile Pro Ala Tyr Gly Lys Arg Thr Gly Ser Ser Phe Leu
65 70 75 80

His Gly Asp Thr Leu Thr Phe Glu Cys Pro Ala Ala Phe Glu Leu Val
85 90 95

Gly Glu Arg Val Ile Thr Cys Gln Gln Asn Asn Gln Trp Ser Gly Asn
100 105 110

Lys Pro Ser Cys Val Phe Ser Cys Phe Phe Asn Phe Thr Ala Ser Ser
115 120 125

Gly Ile Ile Leu Ser Pro Asn Tyr Pro Glu Glu Tyr Gly Asn Asn Met
130 135 140

Asn Cys Val Trp Leu Ile Ile Ser Glu Pro Gly Ser Arg Ile His Leu
145 150 155 160

Ile Phe Asn Asp Phe Asp Val Glu Pro Gln Phe Asp Phe Leu Ala Val
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Lys Asp Asp Gly Ile Ser Asp Ile Thr Val Leu Gly Thr Phe Ser Gly
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Asn Glu Val Pro Ser Gln Leu Ala Ser Ser Gly His Ile Val Arg Leu
195 200 205

Glu Phe Gln Ser Asp His Ser Thr Thr Gly Arg Gly Phe Asn Ile Thr
210 215 220

Tyr Thr Thr Phe Gly Gln Asn Glu Cys His Asp Pro Gly Ile Pro Ile
225 230 235 240

Asn Gly Arg Arg Phe Gly Asp Arg Phe Leu Leu Gly Ser Ser Val Ser
245 250 255

Phe His Cys Asp Asp Gly Phe Val Lys Thr Gln Gly Ser Glu Ser Ile
260 265 270

Thr Cys Ile Leu Gln Asp Gly Asn Val Val Trp Ser Ser Thr Val Pro
275 280 285

Arg Cys Glu Ala Pro Cys Gly Gly His Leu Thr Ala Ser Ser Gly Val
290 295 300

Ile Leu Pro Pro Gly Trp Pro Gly Tyr Tyr Lys Asp Ser Leu His Cys
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Glu Trp Ile Ile Glu Ala Lys Pro Gly His Ser Ile Lys Ile Thr Phe
325 330 335

Asp Arg Phe Gln Thr Glu Val Asn Tyr Asp Thr Leu Glu Val Arg Asp
340 345 350

Gly Pro Ala Ser Ser Ser Pro Leu Ile Gly Glu Tyr His Gly Thr Gln
355 360 365

Ala Pro Gln Phe Leu Ile Ser Thr Gly Asn Phe Met Tyr Leu Leu Phe
370 375 380

Thr Thr Asp Asn Ser Arg Ser Ser Ile Gly Phe Leu Ile His Tyr Glu
385 390 395 400

Ser Val Thr Leu Glu Ser Asp Ser Cys Leu Asp Pro Gly Ile Pro Val
405 410 415

Asn Xaa His Arg His Gly Gly Asp Phe Gly Ile Arg Ser Thr Val Thr
420 425 430

Phe Ser Cys Asp Pro Gly Tyr Thr Leu Ser Asp Asp Glu Pro Leu Val
435 440 445

Cys Glu Arg Asn His Gln Trp Asn His Ala Leu Pro Ser Cys Asp Ala
450 455 460

Leu Cys Gly Gly Tyr Ile Gln Gly Lys Ser Gly Thr Val Leu Ser Pro
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Gly Phe Pro Asp Phe Tyr Pro Asn Ser Leu Asn Xaa Thr Trp Thr Ile
485 490 495

Glu Val Ser His Gly Lys Gly Val Gln Met Ile Phe His Thr Phe His
500 505 510

Leu Glu Ser Ser His Asp Tyr Leu Leu Ile Thr Glu Asp Gly Ser Phe
515 520 525

Ser Glu Pro Val Ala Arg Leu Thr Gly Ser Val Leu Pro His Thr Ile
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Lys Ala Gly Leu Phe Gly Asn Phe Thr Ala Gln Leu Arg Phe Ile Ser
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Asp Phe Ser Ile Ser Tyr Glu Gly Phe Asn Ile Thr Phe Ser Glu Tyr
565 570 575

Asp Leu Glu Pro Cys Asp Asp Pro Gly Val Pro Ala Phe Ser Arg Arg
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Ile Gly Phe His Phe Gly Val Gly Asp Ser Leu Thr Phe Ser Cys Phe
595 600 605

Leu Gly Tyr Arg Leu Glu Gly Ala Xaa Lys Leu Thr Cys Leu Gly Gly
610 615 620

Gly Arg Arg Val Trp Ser Ala Pro Leu Pro Arg Cys Val Ala Glu Cys
625 630 635 640

Gly Ala Ser Val Lys Gly Asn Glu Gly Thr Leu Leu Ser Pro Asn Phe
645 650 655

Pro Ser Asn Tyr Asp Asn Asn His Glu Cys Ile Tyr Lys Ile Glu Thr
660 665 670

Glu Ala Gly Lys Gly Ile His Leu Arg Thr Arg Ser Phe Gln Leu Phe
675 680 685

Glu Gly Asp Thr Leu Lys Val Tyr Asp Gly Lys Asp Ser Ser Ser Arg
690 695 700

Pro Leu Gly Thr Phe Thr Lys Asn Glu Leu Leu Gly Leu Ile Leu Asn
705 710 715 720

Ser Thr Ser Asn His Xaa Trp Leu Glu Phe Asn Thr Asn Gly Ser Asp
725 730 735

Thr Asp Gln Gly Phe Gln Leu Thr Tyr Thr Ser Phe Asp Leu Val Lys
740 745 750

Cys Glu Asp Pro Gly Ile Pro Asn Tyr Gly Tyr Arg Ile Arg Asp Glu
755 760 765

Gly His Phe Thr Asp Thr Val Val Leu Tyr Ser Cys Asn Pro Gly Tyr
770 775 780

Ala Met His Gly Ser Asn Thr Leu Thr Cys Leu Ser Gly Asp Arg Arg
785 790 795 800

Val Trp Asp Lys Pro Leu Pro Ser Cys Ile Ala Glu Cys Gly Gly Gln
805 810 815

Ile His Ala Ala Thr Ser Gly Arg Ile Leu Ser Pro Gly Tyr Pro Ala
820 825 830

Pro Tyr Asp Asn Asn Leu His Cys Thr Trp Ile Ile Glu Ala Asp Pro
835 840 845

Gly Lys Thr Ile Ser Leu His Phe Ile Val Phe Asp Thr Glu Met Ala
850 855 860

His Asp Ile Leu Lys Val Trp Asp Gly Pro Val Asp Ser Asp Ile Leu
865 870 875 880

Leu Lys Glu Trp Ser Gly Ser Ala Leu Pro Glu Asp Ile His Ser Thr
885 890 895

Phe Asn Ser Leu Thr Leu Gln Phe Asp Ser Asp Phe Phe Ile Ser Lys
900 905 910

Ser Gly Phe Ser Ile Gln Phe Ser Thr Ser Ile Ala Ala Thr Cys Asn
915 920 925

Asp Pro Gly Met Pro Gln Asn Gly Thr Arg Tyr Gly Asp Ser Arg Glu
930 935 940

Ala Gly Asp Thr Val Thr Phe Gln Cys Asp Pro Gly Tyr Gln Leu Gln
945 950 955 960

Gly Gln Ala Lys Ile Thr Cys Val Gln Leu Asn Asn Arg Phe Phe Trp
965 970 975

Gln Pro Asp Pro Pro Thr Cys Ile Ala Ala Cys Gly Gly Asn Leu Thr
980 985 990

Gly Pro Ala Gly Val Ile Leu Ser Pro Asn Tyr Pro Gln Pro Tyr Pro
995 1000 1005

Pro Gly Lys Glu Cys Asp Trp Arg Val Lys Val Asn Pro Asp Phe
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Val Ile Ala Leu Ile Phe Lys Ser Phe Asn Met Glu Pro Ser Tyr
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Ala Cys Phe Asp Pro Gly Asn Ile Met Asn Gly Thr Arg Val Gly
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Thr Asp Phe Lys Leu Gly Ser Thr Ile Thr Tyr Gln Cys Asp Ser
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Gly Tyr Lys Ile Leu Asp Pro Ser Ser Ile Thr Cys Val Ile Gly
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Ala Asp Gly Lys Pro Ser Trp Asp Gln Val Leu Pro Ser Cys Asn
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Tyr Ser Ile Thr Val Pro Lys Glu Phe Val Val Phe Gly Gln Phe
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His Ser Gly Glu Thr Leu Pro Leu Ala Thr Ser Asn Gln Ile Leu
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Phe Val Tyr Gln Ala Val Pro Arg Thr Ser Asp Thr Gln Cys Ser
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Ser Val Pro Glu Pro Arg Tyr Gly Arg Arg Ile Gly Ser Glu Phe
1280 1285 1290

Ser Ala Gly Ser Ile Val Arg Phe Glu Xaa Asn Pro Gly Tyr Leu
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Leu Gln Gly Ser Thr Ala Leu His Cys Gln Ser Val Pro Asn Ala
1310 1315 1320

Leu Ala Gln Trp Asn Asp Thr Ile Pro Ser Cys Val Val Pro Cys
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Ser Gly Asn Phe Thr Gln Arg Arg Gly Thr Ile Leu Ser Pro Gly
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Tyr Pro Glu Pro Tyr Gly Asn Asn Leu Asn Cys Ile Trp Lys Ile
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Ile Val Thr Glu Gly Ser Gly Ile Gln Ile Gln Val Ile Ser Phe
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Ala Thr Glu Gln Asn Trp Asp Ser Leu Glu Ile His Asp Gly Gly
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Asp Val Thr Ala Pro Arg Leu Gly Ser Phe Ser Gly Thr Thr Val
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Pro Ala Leu Leu Asn Ser Thr Ser Asn Gln Leu Tyr Leu His Phe
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Gln Ser Asp Ile Ser Val Ala Ala Ala Gly Phe His Leu Glu Tyr
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Lys Thr Val Gly Leu Ala Ala Cys Gln Glu Pro Ala Leu Pro Ser
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Asn Ser Ile Lys Ile Gly Asp Arg Tyr Met Val Asn Asp Val Leu
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Ser Phe Gln Cys Glu Pro Gly Tyr Thr Leu Gln Gly Arg Ser His
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Ile Ser Cys Met Pro Gly Thr Val Arg Arg Trp Asn Tyr Pro Ser
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Leu Asp Cys Thr Trp Arg Ile Ser Leu Pro Ile Gly Tyr Gly Ala
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His Ile Gln Phe Leu Asn Phe Ser Thr Glu Ala Asn His Asp Phe
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Leu Glu Ile Gln Asn Gly Pro Tyr His Thr Ser Pro Met Ile Gly
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Gln Phe Ser Gly Thr Asp Leu Pro Ala Ala Leu Leu Ser Thr Thr
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Tyr Ser Val Gly Gln Ser Val Ser Phe Glu Cys Tyr Pro Gly Tyr
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Tyr Asn Val Thr Ser Gln Asn Gly Thr Ile Tyr Ser Pro Gly Phe
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Pro Asp Glu Tyr Pro Ile Leu Lys Asp Cys Ile Trp Leu Ile Thr
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Glu Met Leu Thr Glu Asp Asp Asp Phe Glu Ile Gly Asp Phe Val
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Lys Tyr Gln Cys His Pro Gly Tyr Thr Leu Val Gly Thr Asp Ile
1820 1825 1830

Leu Thr Cys Lys Leu Ser Ser Gln Leu Gln Phe Glu Gly Ser Leu
1835 1840 1845

Pro Thr Cys Glu Ala Gln Cys Pro Ala Asn Glu Val Arg Thr Gly
1850 1855 1860

Ser Ser Gly Val Ile Leu Ser Pro Gly Tyr Pro Gly Asn Tyr Phe
1865 1870 1875

Asn Ser Gln Thr Cys Ser Trp Ser Ile Lys Val Glu Pro Asn Tyr
1880 1885 1890

Asn Ile Thr Ile Phe Val Asp Thr Phe Gln Ser Glu Lys Gln Phe
1895 1900 1905

Asp Ala Leu Glu Val Phe Asp Gly Ser Ser Gly Gln Ser Pro Leu
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1925 1930 1935

Ser Arg Ser Asn Gln Leu Tyr Leu Arg Trp Ser Thr Asp His Ala
1940 1945 1950

Thr Ser Lys Lys Gly Phe Lys Ile Arg Tyr Ala Ala Pro Tyr Cys
1955 1960 1965

Ser Leu Thr His Pro Leu Lys Asn Gly Gly Ile Leu Asn Arg Thr
1970 1975 1980

Ala Gly Ala Val Gly Ser Lys Val His Tyr Phe Cys Lys Pro Gly
1985 1990 1995

Tyr Arg Met Val Gly His Ser Asn Ala Thr Cys Arg Arg Asn Pro
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Thr Arg Cys Leu Ala Gly His Cys Gly Ser Pro Asp Pro Ile Val
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Cys Val Pro Ile Thr Cys Gly His Pro Gly Asn Pro Ala His Gly
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Phe Thr Asn Gly Ser Glu Phe Asn Leu Asn Asp Val Val Asn Phe
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2495 2500 2505

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2600 2605 2610

Arg Cys Thr Lys Asp Gly Arg Trp Asn Pro Ser Lys Pro Val Cys
2615 2620 2625

Lys Ala Val Leu Cys Pro Gln Pro Pro Pro Val Gln Asn Gly Thr
2630 2635 2640

Val Glu Gly Ser Asp Phe Arg Trp Gly Ser Ser Ile Ser Tyr Ser
2645 2650 2655

Cys Met Asp Gly Tyr Gln Leu Ser His Ser Ala Ile Leu Ser Cys
2660 2665 2670

Glu Gly Arg Gly Val Trp Lys Gly Glu Ile Pro Gln Cys Leu Pro
2675 2680 2685

Val Phe Cys Gly Asp Pro Gly Ile Pro Ala Glu Gly Arg Leu Ser
2690 2695 2700

Gly Lys Ser Phe Thr Tyr Lys Ser Glu Val Phe Phe Gln Cys Lys
2705 2710 2715

Ser Pro Phe Ile Leu Val Gly Ser Ser Arg Arg Val Cys Gln Ala
2720 2725 2730

Asp Gly Thr Trp Ser Gly Ile Gln Pro Thr Cys Ile Asp Pro Ala
2735 2740 2745

His Asn Thr Cys Pro Asp Pro Gly Thr Pro His Phe Gly Ile Gln
2750 2755 2760

Asn Ser Ser Arg Gly Tyr Glu Val Gly Ser Thr Val Phe Phe Arg
2765 2770 2775

Cys Arg Lys Gly Tyr His Ile Gln Gly Ser Thr Thr Arg Thr Cys
2780 2785 2790

Leu Ala Asn Leu Thr Trp Ser Gly Ile Gln Thr Glu Cys Ile Pro
2795 2800 2805

His Ala Cys Arg Gln Pro Glu Thr Pro Ala His Ala Asp Val Arg
2810 2815 2820

Ala Ile Asp Leu Pro Thr Phe Gly Tyr Thr Leu Val Tyr Thr Cys
2825 2830 2835

His Pro Gly Phe Phe Leu Ala Gly Gly Ser Glu His Arg Thr Cys
2840 2845 2850

Lys Ala Asp Met Lys Trp Thr Gly Lys Ser Pro Val Cys Lys Ser
2855 2860 2865

Lys Gly Val Arg Glu Val Asn Glu Thr Val Thr Lys Thr Pro Val
2870 2875 2880

Pro Ser Asp Val Phe Phe Val Asn Ser Leu Trp Lys Gly Tyr Tyr
2885 2890 2895

Glu Tyr Leu Gly Lys Arg Gln Pro Ala Thr Leu Thr Val Asp Trp
2900 2905 2910

Phe Asn Ala Thr Ser Ser Lys Val Asn Ala Thr Phe Ser Glu Ala
2915 2920 2925

Ser Pro Val Glu Leu Lys Leu Thr Gly Ile Tyr Lys Lys Glu Glu
2930 2935 2940

Ala His Leu Leu Leu Lys Ala Phe Gln Ile Lys Gly Gln Ala Asp
2945 2950 2955

Ile Phe Val Ser Lys Phe Glu Asn Asp Asn Trp Gly Leu Asp Gly
2960 2965 2970

Tyr Val Ser Ser Gly Leu Glu Arg Gly Gly Phe Thr Phe Gln Gly
2975 2980 2985

Asp Ile His Gly Lys Asp Phe Gly Lys Phe Lys Leu Glu Arg Gln
2990 2995 3000

Asp Pro Leu Asn Pro Asp Gln Asp Ser Ser Ser His Tyr His Gly
3005 3010 3015

Thr Ser Ser Gly Ser Val Ala Ala Ala Ile Leu Val Pro Phe Phe
3020 3025 3030

Ala Leu Ile Leu Ser Gly Phe Ala Phe Tyr Leu Tyr Lys His Arg
3035 3040 3045

Thr Arg Pro Lys Val Gln Tyr Asn Gly Tyr Ala Gly His Glu Asn
3050 3055 3060

Ser Asn Gly Gln Ala Ser Phe Glu Asn Pro Met Tyr Asp Thr Asn
3065 3070 3075

Leu Lys Pro Thr Glu Ala Lys Ala Val Arg Phe Asp Thr Thr Leu
3080 3085 3090

Asn Thr Val Cys Thr Val Val
3095 3100

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) Internati nal Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/010199 A3

(51) International Patent Classification[7]: C12N 15/12, C07K 14/705, A01K 67/027, A61K 38/16, C07K 16/18, C12N 5/10, 15/62, G01N 33/50

(21) International Application Number: PCT/US01/23232

(22) International Filing Date: 24 July 2001 (24.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/222,504 2 August 2000 (02.08.2000) US
09/728,787 28 November 2000 (28.11.2000) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 11 July 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/010199 A3

(54) Title: C3B/C4B COMPLEMENT RECEPTOR-LIKE MOLECULES AND USES THEREOF

(57) Abstract: Novel C3b/C4b CR-like polypeptides and nucleic acid molecules encoding the same. The invention also provides vectors, host cells, selective binding agents, and methods for producing C3b/C4b CR-like polypeptides. Also provided for are methods for the treatment, diagnosis, amelioration, or prevention of diseases with C3b/C4b CR-like polypeptides.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/705 A01K67/027 A61K38/16 C07K16/18
C12N5/10 C12N15/62 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBL, EPO-Internal, SEQUENCE SEARCH, PAJ, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE EMBL [Online] 19 July 2001 (2001-07-19) SUN, P. ET AL.: "Mus musculus CSMD1 (Csmd1) mRNA, complete cds." retrieved from EBI Database accession no. AY017475 XP002193405 83% identity in 9483 nt overlap (285-9763:1743-11221) with SEQ ID NO:1. abstract 95% identity in 9507 nt overlap (1-9505:1716-11221) with SEQ ID NO:3. 83.6% identity in 9525 nt overlap (1-9523:1701-11221) with SEQ ID NO:6. --- -/--	1-12, 46-48, 55,56

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2002	10. 05. 2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Schmitz, T

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] 14 February 2000 (2000-02-14) BIRREN, B. ET AL.: "Homo sapiens chromosome 2, clone RP11-564K14, complete sequence." retrieved from EBI Database accession no. AC023296 XP002193406 99.7% identity in 1292 nt overlap (10673-9382:84226-85517) with SEQ ID NO:1. abstract 57% identity in 3548 nt overlap (12522-9127:81101-84494) with SEQ ID NO:3. ---	1-12, 46-48, 55,56
P,X	WO 01 36638 A (LICHENSTEIN HENRI ;VERNET CORINE (US); CURAGEN CORP (US); FERNANDE) 25 May 2001 (2001-05-25) SEQ ID NOs:31,32, "NOV16" page 49-53; table 17 60.3% identity in 829 aa overlap (1976-2804:2-830) with SEQ ID NO:2. 65% identity in 2728 nt overlap (5868-8582:294-3007) with SEQ ID NO:3. 60.3% identity in 829 aa overlap (2002-2830:2-830) with SEQ ID NO:4. 60.3% identity in 829 aa overlap (2007-2835:2-830) with SEQ ID NO:7. ---	1-12, 14-20, 22-41, 43-56
X	DATABASE SWALL [Online] 1 November 1999 (1999-11-01) NAGASE, T. ET AL.: "KIAA0927 Protein (Fragment)" retrieved from EBI Database accession no. Q9Y2E1 XP002193407 abstract 32.2% identity in 589 aa overlap (607-1176:331-894) with SEQ ID NO:2. 31% identity in 586 aa overlap (633-1202:331-894) with SEQ ID NO:4. 32.2% identity in 589 aa overlap (638-1207:331-894) with SEQ ID NO:7. ---	15,19, 20, 22-41, 43-45, 49-54
A	WO 98 39433 A (SMITH RICHARD ANTONY GODWIN ;ADPROTECH PLC (GB); COX VIVIENNE FRAN) 11 September 1998 (1998-09-11) the whole document ---	

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International Application No
PCT/US 01/23232

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOURCADE D ET AL: "DUPLICATION AND DIVERGENCE OF THE AMINO-TERMINAL CODING REGION OF THE COMPLEMENT RECEPTOR 1 (CR1) GENE" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 265, no. 2, 15 January 1990 (1990-01-15), pages 974-980, XP002072410 ISSN: 0021-9258 the whole document -----	

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/23232

Box I Observations where certain claims were found unsearchable (Continuation of it m 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1c, 2d, 3f, 14d, 23, 35-39 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 52 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 37, 51, 55 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1c, 2d, 3f, 14d, 23, 35-39 (partially)

Present claims 1c, 2d, 3f, 14d relate to an extremely large number of possible sequences. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the sequences claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the full length of the sequences (SEQ ID NO: 1-4, 6, 7).

Present claims 23, 35-39 relate to a selective binding agent defined by reference to a desirable characteristic or property, namely the binding to an amino acid as defined in SEQ ID NO: 2, 4, 7.

The claims cover all selective binding agents having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such selective binding agent. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the selective binding agent by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the antibodies binding to said polypeptides.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/23232

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0136638	A	25-05-2001	AU	1616801 A	30-05-2001
			WO	0136638 A2	25-05-2001
			AU	6229100 A	05-02-2001
			WO	0105971 A2	25-01-2001
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			EP	0979276 A1	16-02-2000
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			JP	2001516212 T	25-09-2001